Official Title: A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) as Monotherapy and in Combination With Platinum-Based Chemotherapy in Patients With Untreated Locally Advanced or Metastatic Urothelial Carcinoma

NCT Number: NCT02807636

Document Date: SAP Version 3: 15-January-2020

STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS MONOTHERAPY AND IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA**

PROTOCOL NUMBER:	WO30070
STUDY DRUG:	Atezolizumab
VERSION NUMBER:	3
IND NUMBER:	120827
EUDRACT NUMBER:	2016-000250-35
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted], Ph.D
DATE FINAL:	Version 1: 13 December 2018
DATE (S) AMENDED:	Version 2: 25 February 2019 Version 3: See electronic date stamp below

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Date and Time(UTC)	Reason for Signing	Name
15-Jan-2020 08:31:11	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This is Version 3 of the statistical analysis plan for Protocol WO30070. The amendment was prepared in response to health authority feedback following the primary PFS/interim OS analysis, which used data up to the clinical cut-off date of 31 May 2019. In this version, a second interim analysis of OS has been added in order to be able to provide updated results on OS earlier than the final analysis. The efficacy boundaries have been adjusted accordingly based on the pre-specified O'Brien-Fleming alpha spending function. Details are provided in Section 2.5.2.2.

Additional minor changes have been made to improve clarity and consistency.

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study WO30070 (IMvigor130), "A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (anti-programmed death-ligand 1 [PD-L1] antibody) as Monotherapy and in Combination with Platinum-Based Chemotherapy in Patients with Untreated Locally Advanced or Metastatic Urothelial Carcinoma".

2. STUDY DESIGN

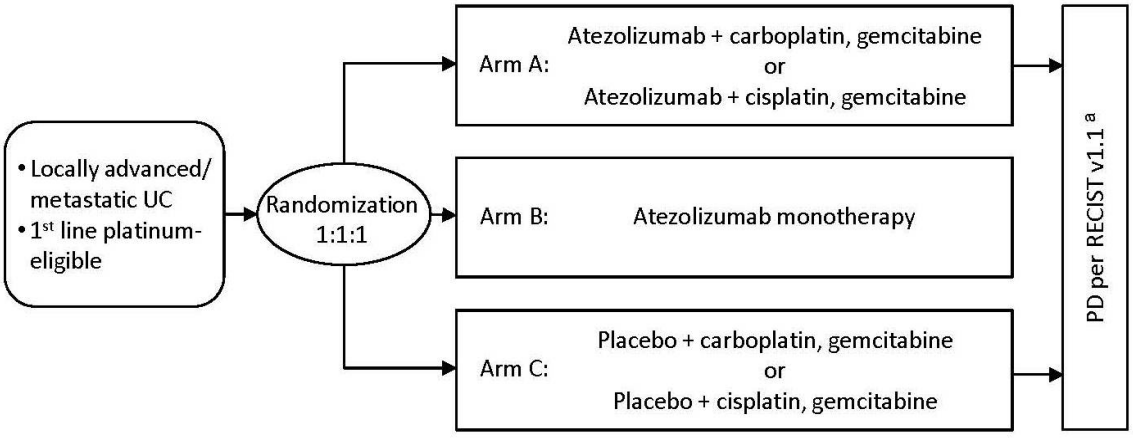
2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. The Protocol Synopsis includes the study objectives and endpoints, study design, inclusion and exclusion criteria, medicinal product administration, and statistical methods for the primary efficacy analysis and planned interim analyses as stated in the protocol. For details of schedule of assessments, see Appendix 2 and Appendix 3.

2.2 CURRENT STUDY DESIGN

IMvigor130 is a Phase III, multicenter, randomized, placebo-controlled, partially blind study designed to evaluate the safety and efficacy of atezolizumab given as monotherapy or in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy (see Figure 1).

Figure 1 Study Schema



PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; UC = urothelial carcinoma.

A total of 1200 patients were planned to be enrolled at approximately 229 sites.

Patients should be considered eligible to receive treatment with platinum-based chemotherapy (either gemcitabine with cisplatin or gemcitabine with carboplatin) and

have measurable disease, defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

A total of 1200 patients were planned to be randomized in a 1:1:1 ratio to receive one of the following:

- Arm A (experimental arm): blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)
- Arm B (experimental arm): open-label atezolizumab monotherapy
- Arm C (control arm): blinded placebo in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)

Prior to randomization, the investigator was to select the chemotherapy the patient receives (gemcitabine and carboplatin vs. gemcitabine and cisplatin) if randomized to Arm A or Arm C. The Galsky criteria (see Protocol Section 4.2) were to be used to guide determination of cisplatin ineligibility.

Randomization was stratified by the following factors:

- PD-L1 status (tumor-infiltrating immune cell 0 [IC0] vs. IC1 vs. IC2/3)
- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)
- Investigator-determined chemotherapy (gemcitabine and carboplatin vs. gemcitabine and cisplatin)

Treatment with platinum-based chemotherapy can continue until progressive disease (PD) per RECIST v1.1 or unacceptable toxicity per investigator discretion. In the case of complete response (CR), only two more cycles of platinum-based chemotherapy may be administered after the response confirmation. In specific circumstances, treatment may continue beyond disease progression (see Protocol Section 4.6.2).

An independent data monitoring committee (iDMC) has been convened to help monitor patient safety (see Protocol Section 3.1.2).

No crossover will be allowed from the control arm to either experimental arm (Arms A and B).

Design Changes

This study was initially implemented with randomization to two treatment arms (carboplatin plus gemcitabine with or without atezolizumab) in patients who were ineligible for cisplatin-based chemotherapy; details of the original design (Protocol Versions 1 and 2) are provided in Section 2.3. In Protocol WO30070 v3, Arm B was added (open-label atezolizumab monotherapy). In addition, the eligibility criteria were expanded to also allow patients who are eligible for cisplatin-based chemotherapy

to enter the study. Protocol WO30070 v3 was implemented while recruitment was ongoing. As a result of this design change, the study consists of two stages: Patients recruited into the study prior to v3 (Stage 1) and patients recruited from Protocol v3 (Stage 2). Patients from both stages will be included in the final analysis.

Based on an ad-hoc review of the survival data of all patients randomized in the study up to 12 March 2018, the study iDMC recommended closure of Arm B (atezolizumab monotherapy) to further accrual of all patients with a PD-L1 expression status of IC0 or IC1 (at this point, enrollment into Stage 1 was complete). The iDMC did not recommend a change in therapy for patients already randomized to atezolizumab monotherapy on study.

The iDMC recommendation also stated that patients with a PD-L1 expression status of IC2/3 could continue to be randomized to Arm A, B, or C and that Arms A and C should remain unchanged (open to all patients regardless of PD-L1 status).

This recommendation was implemented in Protocol WO30070 v6. The study design following implementation of Protocol WO30070 v6 is presented below (see Figure 2).

Stratified randomization to the three arms in a 1:1:1 ratio continued regardless of PD-L1 status.

Prior to randomization, all patients were informed per the consent form that if randomized to Arm B (atezolizumab monotherapy) and determined to have a tumor PD-L1 expression status of IC0 or IC1, they would receive chemotherapy combined with atezolizumab instead of atezolizumab monotherapy. For patients who are found to have a tumor PD-L1 expression status of IC0 or IC1, and are not willing to undergo treatment with atezolizumab with chemotherapy, the consent informed these patients to consider treatment outside of the trial rather than proceeding with trial enrollment.

For all new patients randomized to Arm B (open-label atezolizumab monotherapy) after approval of Protocol WO30070 v6:

- The PD-L1 status was unblinded to the investigator and patient at the time of randomization.
- Patients whose PD-L1 expression status was IC2/3 received atezolizumab monotherapy.
- Patients with a PD-L1 expression status of IC0 or IC1 received open-label atezolizumab plus platinum (carboplatin or cisplatin) and gemcitabine chemotherapy instead of atezolizumab monotherapy.
- If a patient with a PD-L1 expression status of IC0 or IC1 subsequently wished to receive standard-of-care chemotherapy instead of atezolizumab plus platinum and gemcitabine chemotherapy, he/she was able to receive standard-of-care chemotherapy of their choice (provided outside of the protocol) and continue on survival follow up.

For all patients in Arm B currently being treated with open-label atezolizumab monotherapy at the time of approval of Protocol WO30070 v6:

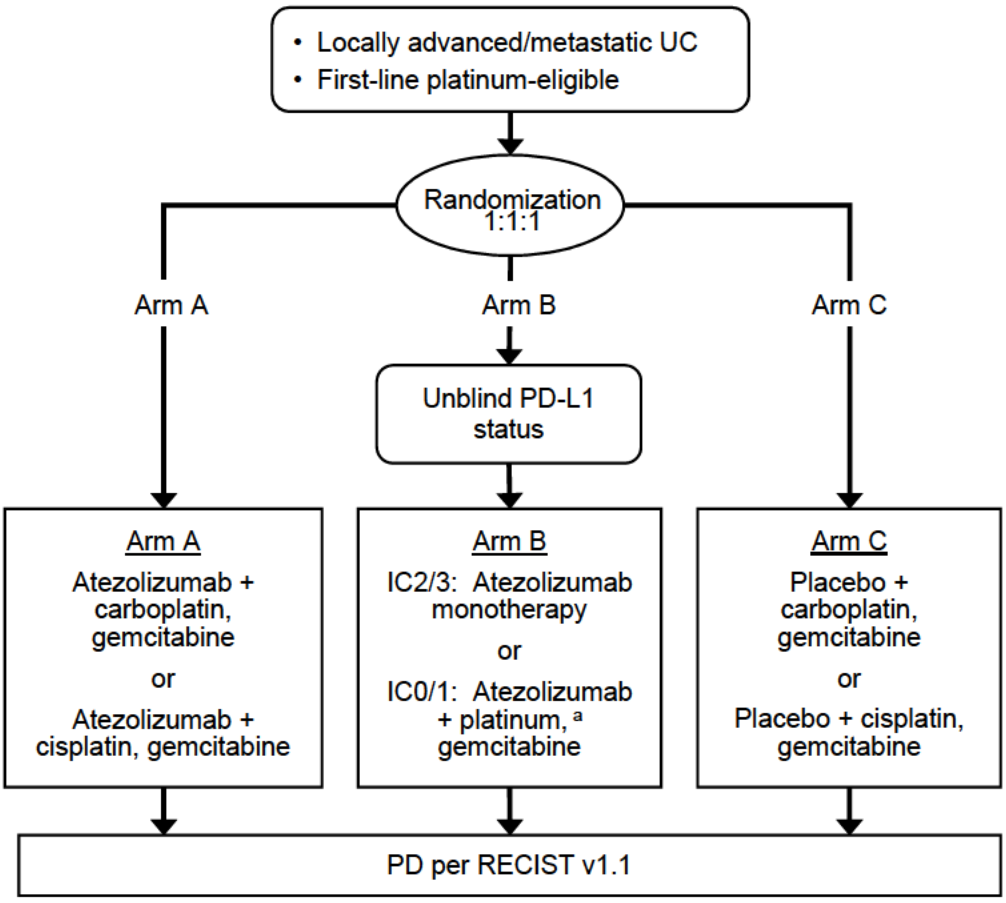
- Patients to be informed that the iDMC has not recommended any changes to therapy for those already randomized to atezolizumab monotherapy.
- The option of unblinding the PD-L1 status upon patient and the investigator request was introduced.
- Patients with PD-L1 expression status of IC2/3 will continue receiving atezolizumab monotherapy.
- Patients with PD-L1 expression status of IC0 or IC1 are recommended to continue with atezolizumab monotherapy, as the iDMC did not recommend a change in therapy for patients already randomized to monotherapy on study.

  However, if the patient after discussion of benefit-risk with the treating physician determines that continuation of atezolizumab monotherapy is not considered beneficial, a treatment alternative of atezolizumab plus platinum (cisplatin or carboplatin) and gemcitabine chemotherapy will be provided. These patients should then be treated the same as patients in Arms A and C (see Protocol Section 4.3.2.2 on duration of chemotherapy).

  If the decision is made to unblind the patient and add platinum (cisplatin or carboplatin) and gemcitabine chemotherapy to the regimen, it should be added before patient has known PD. Chemotherapy should not be added to Arm B patients with documented PD within the study.

- Patients also have the option to stop study therapy and receive standard-of-care treatment outside of the study by their physician.
- All patients (including those who choose to stop atezolizumab monotherapy) are requested to continue in the study for survival follow up.

Figure 2 Study Schema for Patients Randomized into Protocol WO30070, Version 6



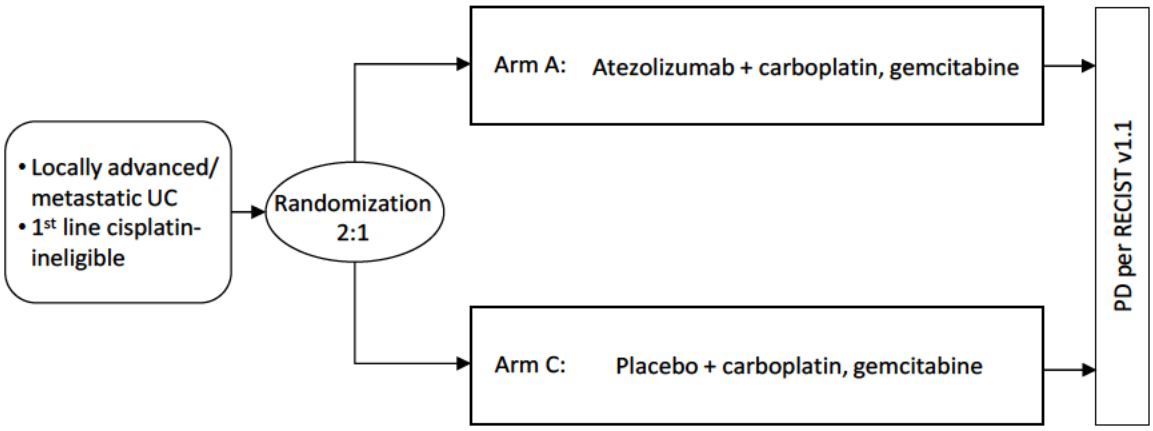
IC = tumor-infiltrating immune cell; PD = progressive disease; PD-L1 = programmed death-ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors; UC = urothelial carcinoma.

[a] Platinum (cisplatin or carboplatin).

2.3 INITIAL 2-ARM STUDY DESIGN (STAGE 1, PRIOR TO PROTOCOL WO30070, VERSION 3)

Study WO30070 was initially implemented with randomization into two treatment arms (carboplatin plus gemcitabine with or without atezolizumab) (see Figure 3).

Figure 3 Study Schema Prior to Protocol Version 3



PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; UC = urothelial carcinoma.

Patients enrolled prior to Protocol WO30070 v3 (Stage 1) were randomized in a 2:1 ratio (experimental to control arm) to receive one of the following:

- atezolizumab in combination with gemcitabine/carboplatin
- placebo in combination with gemcitabine/carboplatin

Randomization was stratified by the following factors:

- PD-L1 status (IC0 vs. IC1 vs. IC2/3)
- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)
- Prior perioperative chemotherapy (neoadjuvant or adjuvant) (yes vs. no)

  Prior perioperative chemotherapy is defined as at least two cycles of combination chemotherapy, such as cisplatin/gemcitabine or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) administered in the neoadjuvant/adjuvant setting or standard radiosensitizing chemotherapy (cisplatin or 5FU/mitomycin) if administered concurrently with radiotherapy.

2.4 DETERMINATION OF SAMPLE SIZE

A total of approximately 1200 patients were planned be randomized to the study. This was based on the following assumptions: approximately 258 patients were projected to be enrolled before approval of Protocol v3 (in Stage 1) and allocated 2:1 to Arm A (atezolizumab in combination with platinum therapy) or Arm C (placebo in combination with platinum therapy). Approximately 942 patients were projected to be enrolled after approval of Protocol v3 (in Stage 2) and allocated 1:1:1 to Arm A, Arm B (atezolizumab monotherapy), or Arm C.

Simulations were performed to check the expected power of the analyses of co-primary endpoints progression-free-survival (PFS) and overall survival (OS) for this sample size as described below.

The definitions of the analysis population are provided in Section 4.1.

2.4.1 Type I Error Control

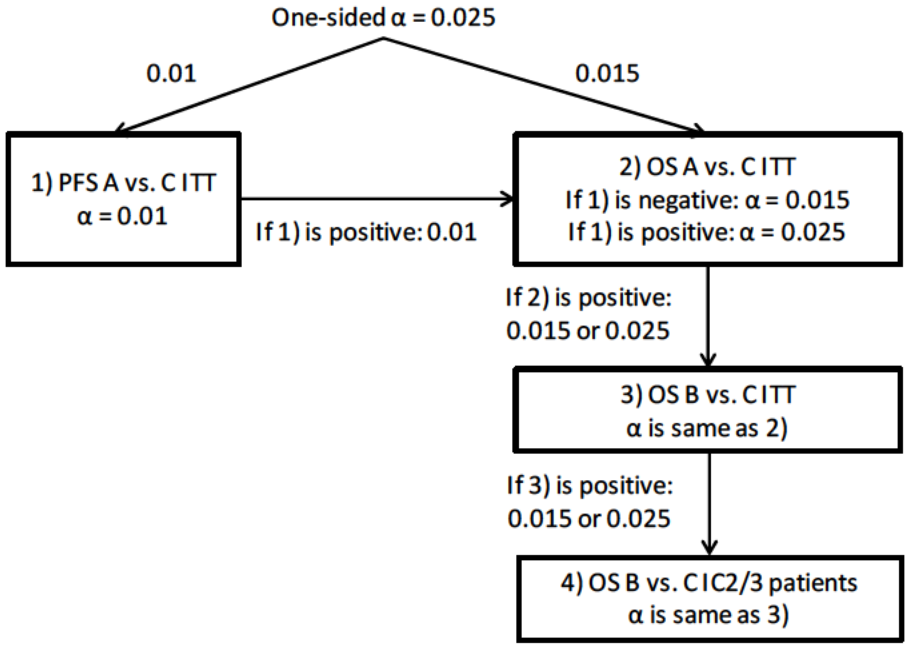
The type I error (α) for this study is 0.025 (one-sided). A one-sided test will be used because of the enrollment in 2 stages (see Section 2.2), and treatment effects could be observed in opposite directions in the 2 stages.

There are two co-primary efficacy endpoints for this study: PFS by investigator assessment per RECIST v1.1 and OS. To control the overall type I error rate while accounting for two co-primary endpoints, α will be split between PFS ($\alpha = 0.01$) and OS ($\alpha = 0.015$) (Figure 4, Bretz et al. 2009). Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

Formal treatment comparisons of PFS and OS in Arm A versus Arm C will be performed in a hierarchical fashion in which α may be recycled as follows (Figure 4, Burman et al. 2009):

1. PFS in Arm A versus Arm C of the intent-to-treat (ITT) population will be evaluated at $\alpha = 0.01$ (one-sided).
2. If PFS results in Arm A versus Arm C of the ITT population are statistically significant at $\alpha = 0.01$, then $\alpha = 0.01$ will be recycled to OS in Arm A versus Arm C of the ITT population, and OS in Arm A versus Arm C of the ITT population will be evaluated at $\alpha = 0.025$ (one-sided). If PFS results in Arm A versus Arm C of the ITT population are not statistically significant at $\alpha = 0.01$, then no recycling of α will occur, and OS in Arm A versus Arm C of the ITT population will be evaluated at $\alpha = 0.015$ (one-sided).
3. OS will also be compared between the ITT population of Arm B and Arm C using a hierarchical approach as follows: If the duration of OS is shown to be statistically significantly longer in Arm A compared to Arm C at the appropriate α level (see Step 2 above), then the duration of OS in the ITT population of Arm B and Arm C will be compared at the same α level. If the OS results for Arm A versus Arm C of the ITT population are not statistically significant, formal treatment comparison of OS in the ITT population of Arm B versus Arm C will not be performed.
4. If the comparison in Step 3 above is statistically significant at the appropriate α level, then OS will be compared between the PD-L1 IC2/3 population of Arm B and Arm C at the same α level.

Figure 4 Progression-Free Survival and Overall Survival Analysis Hierarchy, Alpha Allocation and Alpha Recycling



A=Arm A; B=Arm B; C=Arm C; IC=tumor-infiltrating immune cell; ITT=intent-to-treat; PFS=progression-free survival; OS=overall survival.

It is important to note that the decision to change from a two-arm to a three-arm design (see Section 2.2 and Section 2.3) was informed by external information only. At the time of the decision, there were less than 5 patients enrolled in Stage 1 of the study, and there was no interim look at study data prior to the protocol amendment. Additionally, the two-arm study was placebo-controlled, and the Sponsor had no access to treatment codes assigned at randomization. Therefore, the change does not result in inflation of the type I error.

While there will only be one formal analysis of PFS, two interim analyses of OS will be performed; the first one at the same time as the final PFS analysis, regardless of the outcome of the PFS analysis. The second interim OS analysis will be performed approximately 12 months after the first, or when at least 579 patients (68%) have died in Arm A and Arm C, whichever is later. The methods to control the overall type I error during the interim and final analyses of OS are described in Section 2.5.2.2.

2.4.2 Co-primary Endpoint: PFS

The duration of PFS will be compared between Arm A and Arm C. The projected number of patients in the ITT population for the comparison of Arm A versus Arm C was 886 patients at the time of implementation of Protocol v3.

The analysis of the co-primary endpoint of PFS will take place when approximately 667 PFS events in the ITT population for the comparison of Arm A versus Arm C have occurred (75% of 886 randomized patients) on the basis of the following assumptions:

- Stratified log-rank test combining data from Stage 1 and Stage 2
- $\alpha = 0.01$ (significance level for combined p-value, one-sided)
- Approximately 91% power
- Median PFS in the control arm of 6.8 months and estimated median PFS in the atezolizumab plus chemotherapy arm of 9.1 months (an increase of 2.3 months, corresponding to a hazard ratio [HR] of 0.75)
- Dropout rate of 5% annually
- No interim analysis of PFS

2.4.3 Co-Primary Endpoint: Overall Survival

The co-primary endpoint of OS will be compared between Arms A and C, and between Arms B and C in a hierarchical fashion as described in Section 2.4.1.

Arm A versus Arm C

The projected number of patients in the ITT population for the comparison of Arm A versus Arm C was 886 patients at the time of implementation of Protocol v3.

The final analysis will take place when approximately 667 OS events in the ITT population for the comparison of Arm A versus Arm C of the global enrollment phase of the study have occurred (75% of 886 randomized patients) on the basis of the following assumptions:

- Stratified log-rank test combining data from Stage 1 and Stage 2
- $\alpha = 0.015$ (one-sided)
- Approximately 99% power
- Median OS in the control arm of 12 months and estimated median OS in the atezolizumab plus chemotherapy arm of 17.1 months (an increase of 5.1 months, corresponding to a HR of 0.70)
- Dropout rate of 5% annually
- One interim analysis to be performed at the time of the PFS analysis (see Section 2.5.2.2)

Note that the addition of a second interim analysis (see Section 2.5.2) does not result in a noticeable reduction of statistical power.

Arm B versus Arm C

Prior to the iDMC recommendation to stop further recruitment of patients with PD-L1 status of IC0 or IC1 to atezolizumab monotherapy (see Section 2.2), the statistical power was determined as follows. The expected number of patients for the comparison of Arm B versus Arm C, defined as all patients concurrently randomized during Stage 2 of the study, was approximately 628 patients. The final analysis was planned when approximately 471 OS events in the ITT population for Arm B and Arm C in the global enrollment phase of the study have occurred (75% of 628 patients) on the basis of the following assumptions:

- Stratified log-rank test using data from Stage 2 patients only
- $\alpha = 0.015$ (one-sided)
- Approximately 88% power
- Median OS in the control arm of 12 months and estimated median OS in the atezolizumab arm of 16.4 months (an increase of 4.4 months, corresponding to a HR of 0.73)
- Dropout rate of 5% annually
- One interim analysis to be performed at the time of the PFS analysis (see Section 2.5.2.2)

In Protocol v6, enrollment into Arm B was modified according to a recommendation from the iDMC (see Section 2.2), which was expected to reduce the sample size. In order to ensure sufficient follow-up at the time of the final OS analysis in Arm B versus Arm C, the proportion of patients who will have died by the time of the final analysis was kept at 75% as in the original design.

An additional formal comparison of OS in patients in Arm B versus Arm C with a PD-L1 status of IC2/3 is included in the testing hierarchy, see Figure 4. However, this test was not taken into account for determining the sample size.

2.5 INTERIM AND PRIMARY ANALYSIS TIMING

Note that the actual enrollment into Stage 1 and 2 was different from the numbers used for the projections of the analysis timing in the protocol and in the SAP, Section 2.4, which were performed during the early stages of recruitment. The estimated analysis timing for the second interim OS analysis and the final OS analysis that are described in this section is based on actual enrollment and updated projections after the final PFS analysis/first interim OS analysis.

The definitions of the analysis populations are provided in Section 4.1.

2.5.1 Primary Analysis Timing

The analysis of the co-primary endpoint of **PFS in Arm A versus Arm C** will take place when approximately 667 PFS events have occurred in the ITT population for comparisons of Arm A versus Arm C (in 78% of approximately 852 patients, see Section 4.1.1). Based on the assumptions for median PFS and drop-out rate described in Section 2.4.2 and patient accrual, the required number of PFS events is projected to occur at Month 35 from the time the first patient was randomized.

The study will be unblinded at the time of the primary PFS analysis.

The final analysis of the co-primary endpoint of **OS in Arm A versus Arm C** will take place when approximately 667 deaths have occurred in the ITT population for Arm A versus Arm C (in 78% of approximately 852 patients). Based on observed survival up to the final PFS/interim OS analysis, the required number of events is projected to occur at Month 55 from the time the first patient was randomized, i.e., approximately 5 months later than according to the projections in the initial SAP.

The final analysis of the co-primary endpoint of **OS in Arm B versus Arm C** will take place at the later of two time points:

1. when 75% of the approximately 719 patients in the ITT population for comparisons of Arm B versus Arm C have died, i.e., after approximately 539 deaths have been reported
2. at the time of the final analysis of OS in Arm A versus. Arm C; in this scenario, the number of deaths reported in the ITT population for Arm B and Arm C is expected to be >539.

This timing for the final analysis of OS in Arm B versus Arm C may be adjusted under certain circumstances, such as

- the projected cut-off date under the two scenarios above is less than 3 months apart
- too few patients still at risk in order to meaningfully increase the observed number of deaths with longer follow-up.

In these cases, the clinical cut-off date for the analysis of OS in Arm B versus Arm C will be the same as that used for the analysis of OS in Arm A versus Arm C.

In addition, OS will be compared in Arm B versus Arm C in the subgroup of patients with PD-L1 score of IC 2 or 3 (see Figure 4). This analysis will be performed at the same time as that in the whole ITT for comparisons of Arm B versus Arm C. The number of patients in the PD-L1 IC2/3 population for OS comparisons of Arm B versus Arm C is 173 patients.

2.5.2 Interim Analysis Timing

There is no interim analysis of PFS.

2.5.2.1 Ad hoc Interim OS Analysis

An ad hoc OS interim analysis will be performed in order to respond to a request from the FDA in June 2018. The request was for a futility analysis for the comparison of OS between Arm B and Arm C to be performed prior to the time of the planned final PFS analysis comparing Arm A and Arm C.

The clinical cut-off for this analysis is 16 October 2018.

The analysis will be performed by the independent data coordinating center (iDCC) and reviewed by the iDMC (see also Section 3.3). The Sponsor Study Management Team (SMT) will remain blinded to results of the study until the study unblinding at the time of the primary PFS analysis. The analysis population will be the same as the primary analysis population for the comparison of Arm B versus Arm C as specified in Section 4.1. The futility criterion will be based on the point estimate of the stratified OS HR for OS in Arm B versus Arm C. The statistical analysis method for calculation of the HR, including stratification factors, will be the same as for the primary analysis of OS as described in Section 4.4.2.2.

A value for the OS HR of >1.60 favoring the chemotherapy control over atezolizumab monotherapy will be considered evidence suggestive of futility of treatment with atezolizumab monotherapy compared to chemotherapy control.

If the futility criterion is met, the following additional analysis will be performed by the iDCC. The value for the OS HR comparison of Arm B and Arm C will be obtained for the subgroup of patients followed for at least one year, i.e., patients randomized up to and including 17 October 2017. The futility criterion described above will be applied to this subgroup of patients with the longest follow up.

If the futility criterion is met, the Sponsor Data Review Board (DRB) will work with the iDMC and iDCC on further analyses to better understand the data and evaluate changes to the study conduct that would be considered, if any. Additional analyses may be performed at Sponsor DRB's request, regardless of the outcome of the futility analysis, if needed as part of the response to FDA's request for the futility analysis. The results of the futility analyses will be considered advisory by the Sponsor DRB. The Sponsor DRB will decide on actions to be taken by the Sponsor, if any, based on the outcome of these analyses.

This analysis was not preplanned in the protocol. Protocol Section 6.8.2 states that optional interim analyses may be performed and that the rationale, timing, and statistical details for such an analysis will be documented in the SAP prior to the analysis. Since this interim analysis will not result in early stopping for efficacy, no type I error adjustment is required.

2.5.2.2 Interim OS Efficacy Analyses

Except for the ad hoc interim OS analysis described above, all efficacy analyses, including the interim efficacy analyses of OS will be performed by the Sponsor.

OS comparison of Arm A versus Arm C

A total of three analyses of OS comparing Arm A versus Arm C will be performed (two interim analyses and one final analysis; see Table 1).

The first interim analysis of OS in Arm A versus Arm C was performed as planned at the time of the primary PFS analysis, regardless of the outcome of the PFS analysis. At this time, the study was unblinded to the Sponsor. A total of 463 OS events were observed in Arm A and Arm C (54% of 851 patients). The second interim OS analysis will take place after a minimum of approximately 12 months of additional follow-up compared to the clinical cut-off date for the primary analysis, which was 31 May 2019. The projected number of events in Arm A and C by this time is approximately 600 (71% of patients). If, however, based on subsequent event-tracking, less than 579 events (68% of patients) are projected to have occurred by 31 May 2020, the clinical cut-off date for the second interim analysis will be delayed until this minimum threshold is met.

According to the type I error allocation between co-primary endpoints PFS and OS (see Figure 4), the overall one-sided type I error level for OS will be 0.025 since the PFS result was significant. The methods for the statistical hypothesis test are described in Section 4.4.2. The boundary for statistical significance at the interim and final analyses will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function to maintain this overall type I error rate.

For example, if 600 deaths have occurred at the time of the second OS interim analysis in Arm A versus Arm C, statistical significance will be declared if the one-sided p-value is ≤ 0.016 (Table 1). This p-value boundary for statistical significance is based on the number of projected events; actual boundary p-values will be calculated at the time of analysis based on the actual number of events observed in the ITT population for comparisons of Arm A versus Arm C.

OS comparison of Arm B versus Arm C

The total number of analyses of OS comparing Arm B versus Arm C will be 3 or 4 (2 or 3 interim analyses and one final analysis).

The first interim analysis of OS comparing Arm B versus Arm C was performed at the time of the primary PFS analysis and the second will be at the same time as the second interim OS analysis comparing Arm A versus Arm C.

A third interim analysis of OS in Arm B versus Arm C may be conducted at the time of the final analysis of OS in Arm A versus Arm C in case the number of deaths reported at

this time has not yet reached 75% of patients in the ITT population for comparisons of Arm B versus Arm C, see Section 2.5.1. The final analysis of OS in Arm B versus Arm C would then take place once approximately 75% of patients have died.

A formal comparison of OS in Arm B versus Arm C will only be performed after the OS result in Arm A versus Arm C was significant. If the result for OS in Arm A versus Arm C is significant at the interim analysis, but the result in Arm B versus Arm C is not, then the study will not be stopped, and OS in Arm B versus Arm C will be tested again at the time of the final analysis.

According to the testing hierarchy (see Figure 4), the overall available one-sided type I error level for the comparison of OS in Arm B versus Arm C will be the same as above for the comparison of OS in Arm A versus Arm C (0.025). The boundary for statistical significance at the interim and final analyses of OS in Arm B versus Arm C will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function to maintain this overall type I error rate.

The p-value boundaries for statistical significance shown in Table 1 are based on the number of projected events; actual boundary p-values will be calculated at the time of analysis based on the actual number of events observed in the ITT population for comparisons of Arm B versus Arm C.

If a third interim analysis of OS in Arm B versus Arm C is performed at the time of the final analysis of OS in Arm A versus Arm C, then the corresponding boundary p-value will be determined using the same alpha spending function approach.

As described in Section 2.5.1, the timing of the final analysis of the co-primary endpoint of OS in Arm B versus Arm C depends on both the proportion of events observed in Arm B versus Arm C as well as that in Arm A versus Arm C. If the final analysis in Arm B versus Arm C is performed at the same time as that in Arm A versus Arm C, then it is expected that more than 75% of patients in the ITT population for Arm B versus Arm C will have died at that time. In this case, the p-value boundary at the final analysis of OS in Arm B versus Arm C will be recalculated taking into account the actual information fraction at the respective analysis time points. The methodology was described by Wassmer and Brannath (Wassmer and Brannath 2016, Chapter 3.3). Of note, since the decision on the timing of the final analysis is based on criteria independent of the OS results in Arm B versus Arm C, the overall type I error remains protected.

OS comparison of Arm B vs. Arm C in PD-L1 IC2/3 population

A formal comparison of OS in Arm B versus Arm C in the PD-L1 IC2/3 population will only be performed after the OS result in the ITT population for Arm B versus Arm C was significant.

According to the testing hierarchy (see Figure 4), the overall available one-sided type I error level for the comparison of OS in Arm B versus Arm C will be the same as above for the comparison of OS in the ITT population for Arm B vs. Arm C (0.025). The boundary for statistical significance at the interim and final analyses of OS in the PD-L1 IC2/3 population for comparisons of Arm B versus Arm C will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function to maintain this overall type I error rate.

The p-value boundaries for statistical significance shown in Table 1 are based on the number of projected events; actual boundary p-values will be calculated at the time of analysis based on the actual number of events observed in the PD-L1 IC2/3 population for comparisons of Arm B versus Arm C.

If a third interim analysis of OS in the PD-L1 IC2/3 population of Arm B versus Arm C is performed at the time of the final analysis of OS in Arm A versus Arm C, then the corresponding boundary p-value will be determined using the same alpha spending function approach.

As described above for the analysis of OS in the ITT population for Arm B versus Arm C, in case the actual number of events observed differs from the projected number, the p-value boundary at the time of the final analysis in Arm B versus Arm C in the PD-L1 IC2/3 population will be determined based on the actual number of events observed (Wassmer and Brannath 2016, Chapter 3.3).

Table 1 Overall Survival Interim and Final Analysis Characteristics

	Number of Patients	Number of Events (% Patients)	Information Fraction	p-Value Boundary
Month 35 – final PFS / first interim OS analysis (PFS event-driven)				
First interim OS A vs. C	851	463 (54%)	69%	0.007
First interim OS B vs. C	719	389 (54%)	72%	0.008
First interim OS B vs. C IC2/3	173	75 (43%)	58%	0.003
Month 47 – second interim OS analysis Arm A vs. C (~12 months after first interim OS)				
Second interim OS A vs. C	851	600 (71%) [a]	90%	0.016
Second interim OS B vs. C	719	510 (71%) [a]	95%	0.019
Second interim OS B vs. C IC2/3	173	100 (58%) [a]	77%	0.010
Month 55 – projected time of final OS analysis Arm A vs. C (OS event-driven)				
Final OS A vs. C	851	667 (78%)	100%	0.019
Final OS B vs. C	719	539 (75%) [b]	100%	0.018
Final OS B vs. C IC2/3	173	130 (75%) [b]	100%	0.022

A = ARM A; B = Arm B; C = Arm C; OS = overall survival; PFS = progression-free survival.

Month 1 = month the first patient was randomized.

[a] Projected number; the actual boundary for statistical significance to be calculated at the time of the analysis based on actual number of observed events.

[b] In case final analysis occurs later (> 75% events/patients, see Section 2.5.1), final boundary for statistical significance to be calculated based on actual number of events, see Chapter 3.3 in Wassmer and Brannath 2016.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

The randomization scheme was different before and after Protocol v3 (Stage 1 and 2, respectively), see Section 2.2 and Section 2.3.

During Stage 1, eligible patients were randomized in a 2:1 ratio to receive either

- atezolizumab in combination with gemcitabine and carboplatin
- placebo in combination with gemcitabine and carboplatin

A stratified permuted-block randomization scheme was implemented with the following factors:

- PD-L1 status (IC0 vs. IC1 vs. IC2/3)
- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)
- Prior perioperative chemotherapy (neoadjuvant or adjuvant) (yes vs. no)

Prior perioperative chemotherapy is defined as at least two cycles of combination chemotherapy, such as cisplatin/gemcitabine or MVAC administered in the neoadjuvant/adjuvant setting or standard radiosensitizing chemotherapy (cisplatin or 5FU/mitomycin) if administered concurrently with radiotherapy.

During Stage 2, eligible patients were randomized in a 1:1:1 ratio to receive either

- blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)
- open-label atezolizumab monotherapy
- blinded placebo in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)

A stratified permuted-block randomization scheme was implemented with the following factors:

- PD-L1 status (IC0 vs. IC1 vs. IC2/3)
- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)
- Investigator-determined chemotherapy (gemcitabine and carboplatin vs. gemcitabine and cisplatin)

3.2 INDEPENDENT REVIEW FACILITY

The imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints by an Independent Review Facility (IRF). The IRF will evaluate tumor assessments for determination of progression according to RECIST v1.1. Investigator tumor assessments will not be reconciled with the IRF tumor assessments. Further details will be included in the IRF Charter.

3.3 INDEPENDENT DATA MONITORING

An iDMC was convened to evaluate safety data during the study. Members of the iDMC are external to the Sponsor and are following a charter that outlines their roles and responsibilities. The iDMC was to conduct its first review of safety data when 20 patients have completed at least one cycle of study treatment. The iDMC continued to evaluate study safety data on a periodic basis, approximately every 3 months until 1 year after the enrollment of the first patient in Protocol WO30070 v3. After that period, reviews are conducted approximately every 6 months until the time of the analysis of the co-primary efficacy endpoint of PFS. The Sponsor remains blinded to the results until the analysis of the co-primary endpoint of PFS occurs.

All summaries and analyses for the iDMC review are prepared by treatment arm by an external iDCC. The safety data include demographic data, adverse events (AEs), serious adverse events (SAE), and relevant laboratory data. Following their data review,

the iDMC provides a recommendation to the Sponsor according to the iDMC Charter. The final decision on any changes to the protocol rests with the Sponsor.

Any outcomes of these safety reviews that affect study conduct are to be communicated in a timely manner to the investigators for notification of the Institutional Review Boards/Ethics Committees (IRBs/ECs).

The FDA requested an unplanned ad hoc OS interim analysis to be performed prior to the final PFS analysis. The Sponsor will remain blinded to the result. The analysis will be performed by the iDCC and reviewed by the iDMC, see Section 2.5.2.1 for details.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

The study population consists of two enrollment stages, see Section 2:

- Stage 1: This study was initially implemented with two treatment arms (carboplatin plus gemcitabine with or without atezolizumab, Arm A and Arm C) in patients who are ineligible for cisplatin-based therapy.
- Stage 2: In Protocol WO30070 v3, a third treatment arm was added (atezolizumab monotherapy, Arm B). In addition, the eligibility criteria were expanded to also allow patients who are eligible for cisplatin-based chemotherapy to enter the study.

At the time Protocol v3 was submitted, enrollment was ongoing, and therefore the actual number of patients randomized in each stage is different from the estimates provided in Protocol v3.

4.1.1 ITT Population

For the comparison of efficacy in Arm A versus Arm C, the ITT population is defined as all patients randomized to Arm A or Arm C in Stages 1 and 2, whether or not the assigned study treatment was received.

For the comparison of efficacy in Arm B versus Arm C, the ITT population includes only patients concurrently enrolled in Stage 2 and only those who had been randomized at the time of approval of Protocol WO30070 v6.

The table below summarizes the approximate numbers of patients per enrollment stage and arm and the resulting approximate size of the ITT populations.

Table 2 Overview of ITT Analysis Population

		Arm A	Arm B		Arm C		
	Total	ITT A vs. C		ITT B vs. C		Only ITT A vs. C	ITT A vs. C and B vs. C
Total Randomized	1213	447	**361**		**404**		
Stage 1 (2:1 ratio A:C)	129	86	-			43	
Stage 2 (1:1:1 ratio A:B:C)	1084	361	361		361		
Before Protocol V6	1078	359		359			359
Protocol V6	6	2	2			2	
ITT A vs. C	852	447				404	
ITT B vs. C	719	-		359			359

ITT = intent-to-treat.
A = ARM A; B = Arm B; C = Arm C.
Table shows rounded estimates based on enrollment and randomization ratio.

4.1.2 PD-L1 IC2/3 Population

The PD-L1 IC2/3 population for the comparison of Arm B versus Arm C is defined as all patients randomized in Stage 2 with a PD-L1 status of IC2/3. This includes patients who were randomized to Arm B or Arm C after implementing the iDMC recommendation in Protocol WO30070 v6.

4.1.3 Measurable Disease Population

The measurable disease populations are defined as patients in the respective ITT populations with at least one measurable lesion according to RECIST v1.1 based on investigator assessment.

4.1.4 Duration of Response-evaluable Population

The duration of response (DOR)-evaluable population is defined as patients with an objective response.

4.1.5 Pharmacokinetic-Evaluable Population

The pharmacokinetic (PK)-evaluable population is defined as all patients dosed with atezolizumab who have at least one post-baseline PK result.

4.1.6 Safety Population

The safety population is defined as patients who received any amount of any component of study treatment. Patients will be analyzed according to the treatment received. In particular, patients randomized to Arm B after approval of Protocol WO30070 v6 who received open-label atezolizumab and chemotherapy will be pooled with patients in Arm A for safety analyses.

4.1.7 Patient-Reported Outcome Population

The patient reported outcome (PRO)-evaluable population is defined as patients in the respective ITT populations for comparisons of Arm A versus Arm C and Arm B versus Arm C who have a baseline and at least one post-baseline assessment.

4.2 ANALYSIS OF STUDY CONDUCT

Enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria, and reasons for discontinuation from the study will be summarized overall and by treatment arm for the ITT populations for comparisons of Arm A versus Arm C, Arm B versus. Arm C, and the PD-L1 IC2/3 population for the comparison of Arm B versus Arm C. Study treatment administration and reasons for discontinuation from study treatment will be summarized for the safety population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics (e.g., age, sex, and race/ethnicity), baseline disease characteristics (e.g., Eastern Cooperative Oncology Group [ECOG] performance status, hemoglobin, time from prior chemotherapy) and stratification factors (Bajorin model risk factor score/liver metastasis, investigator choice of chemotherapy, and PD-L1 immunohistochemistry [IHC] IC status) will be summarized by treatment arm for the ITT populations and for subpopulations as appropriate, see Section 4.4.6.

Baseline values are the last available data obtained prior to the patient receiving the first dose of any component of the study treatment on Cycle 1, Day 1 (or at screening, for patients who were not treated), unless otherwise noted. Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be presented for continuous variables, and frequencies and percentages will be presented for categorical variables.

4.4 EFFICACY ANALYSIS

Patients will be grouped for efficacy analyses according to the treatment assigned at randomization, whether or not the assigned treatment was received.

4.4.1 Co-primary Efficacy Endpoint PFS

PFS is defined as the time from randomization to the first documented disease progression as determined by the investigator with the use of RECIST v1.1, or death from any cause, whichever occurs first.

Data for patients who are alive and have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment at which they were known to be progression free. Data for patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day. The primary analysis of PFS will be analyzed in the ITT population for comparisons of Arm A versus Arm C.

For U.S. registrational purposes, the primary analysis of PFS will be defined as described above, with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more consecutive scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

Stratification Factors

The stratification factors will be obtained from the values entered in the Interactive Voice/Web Response System (IxRS) at the time of randomization. As stated in the protocol, to avoid small or zero cell sizes for some of the strata, the stratification factors for Stage 1 and Stage 2 may be combined. For analysis purposes, the stratification factors will be as described below, see Table 3. Specifically, 'prior perioperative chemotherapy' will not be included as a stratification factor in the analyses; the stratification factor of 'investigator choice of chemotherapy' does not apply in Stage 1 because all patients receive carboplatin plus gemcitabine.

Table 3 Baseline Stratification Factors Used in Primary Analysis

Stratification Factor [a]	Randomization						Analysis					
	Stage 1			Stage 2			Stage 1			Stage 2		
Prior perioperative chemotherapy	Yes		No	-			-			-		
Investigator choice of chemotherapy [a]	-		-	Cis/Gem		Carbo/ Gem	-		-	Cis/Gem		Carbo/ Gem
PD-L1 Status	IC0	IC1	IC2/3	IC0	IC1	IC2/3	IC0	IC1	IC2/3	IC0	IC1	IC2/3
Bajorin score/liver metastases [b]	0	1	2	0	1	2	0	1	2	0	1	2

IC = tumor-infiltrating immune cell; PD-L1 = programmed death-ligand 1.

[a] Cis/Gem = cisplatin + gemcitabine vs. Carbo/Gem = carboplatin + gemcitabine; all Stage 1 patients were treated with carboplatin + gemcitabine.

[b] Bajorin model risk factor score/ presence of liver metastases (0 = score 0 and no liver metastases vs. 1 = score 1 and no liver metastases vs. 2 = score 2 and/or liver metastases.

P-value Combination

The analysis will be performed in the ITT Population for Arm A versus Arm C. Treatment comparisons will be based on the stratified log-rank test at the one-sided level of significance of 0.01, see in Section 2.4.1. The stratification factors will be as described above.

A possible effect of study stage will be taken into account as follows: The null hypothesis will first be tested in each of the two stages separately, and both one-sided p-values will be calculated (p_1 and p_2 for Stage 1 and 2, respectively). A combined

p-value will be calculated using the inverse normal approximation (Wassmer 2006) for the combined test statistic:

$$z_{\text{Stage 1+2}} = w_1\, \Phi^{-1}(1-p_1) + w_2\, \Phi^{-1}(1-p_2)$$

Here w_1 and w_2 are the pre-specified weights, where $w_1^2 + w_2^2 = 1$. The weights were determined prior to unblinding and were based on the *projected* number of events at the time of the analysis. If d_1 and d_2 are the projected number of events in Stage 1 and Stage 2, then:

$$w_1 = (\, d_1 / (d_1 + d_2\,))^{½} \quad , \quad w_2 = (\, 1 - w_1^2)^{½}$$

The weights were determined using the following assumptions:

- Number of PFS events triggering final analysis: 667
- Estimated number of patients in ITT population for Arm A versus Arm C: N = 852
- Of those, approximately 129 were randomized 2:1 to Arm A and Arm C during Stage 1 over a duration of 14 months between July 2016 and August 2017
- The remaining approximately 723 patients were randomized 1:1 to Arm A and Arm C during Stage 2 over a duration of 19 months between January 2017 and July 2018
- Median duration of PFS 6.8 months in Arm C and 9.1 months in Arm A
- Dropout rate of 5% annually

Using simulations, the projected number of PFS events at the time of the final analysis is approximately 112 and 555 in Stage 1 and 2, respectively (17% and 83%, respectively, of 667 total events). The resulting values for the weights to be used in the inverse normal p-value combination are:

$$w_1 = (112 / 667)^{½} = 0.410, \quad w_2 = (1 - w_1^2)^{½} = 0.912$$

The values to be used for the primary PFS analysis are summarized in the table below.

Table 4 Inverse Normal p-Value Combination for PFS Arm A vs. Arm C (ITT)

	Stage 1	Stage 2	Combined
Number of Patients	129	723	852
Number of Events	112	555	667
Weights	0.410	0.912	-
p-value	p_1	p_2	$1 - \Phi\,[\, 0.410\, \Phi^{-1}(1-p_1) + 0.912\, \Phi^{-1}(1-p_2)\,]$

ITT = intent-to-treat; PFS = progression-free survival.

Table shows estimates based on enrollment rates, randomization ratio, median PFS of 6.8 and 9.1 months in Arm A and C, respectively, 5% drop-out annually.

PFS Hazard Ratio

The HR, λ_A/λ_C, where λ_A and λ_C represent the hazard of a PFS event in Arm A and Arm C, respectively, will be estimated using a stratified Cox regression model on pooled data from Stage 1 and 2. The stratification variables will be those used for the stratified log-rank test + enrollment stage. The 95% CI for the HR will be provided. Results from analyses stratified only by enrollment stage or unstratified will also be provided. HR < 1 indicates treatment benefit in favor of atezolizumab plus chemotherapy.

Kaplan-Meier methodology will be used to construct PFS-event-free curves for both treatment arms and to estimate median PFS for both treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS.

4.4.2 Co-primary Efficacy Endpoint Overall Survival

4.4.2.1 OS in Arm A vs. Arm C

OS is defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The statistical methods for the comparison of OS in Arm A versus Arm C and the stratification factors will be the same as those described for PFS in Section 4.4.1.

The corresponding weights for the inverse normal p-value combination were determined using the following assumptions:

- Number of deaths triggering final analysis: 667
- Estimated number of patients in ITT population for Arm A versus Arm C: N = 852
- Of those, approximately 129 were randomized 2:1 to Arm A and Arm C during Stage 1 over a duration of 14 months between July 2016 and August 2017
- The remaining approximately 723 patients were randomized 1:1 to Arm A and Arm C during Stage 2 over a duration of 19 months between January 2017 and July 2018
- Median duration of OS 12 months in Arm C and 17.1 months in Arm A
- Dropout rate of 5% annually

Using simulations, the projected number of deaths at the time of the interim and final analysis was determined as above for PFS. The resulting weights for the first interim and final OS analysis were calculated prior to unblinding of the study Table 5. The weights to be used for the second interim OS analysis will be the same as those that were pre-specified for the first interim analysis, summarized in the table below. They were not recalculated based on projected events at the second interim OS because the

Sponsor was already unblinded at the time the second interim analysis was added to this SAP.

Table 5 Inverse Normal p-Value Combination for OS Arm A vs. Arm C (ITT)

	Stage 1	Stage 2	Combined
Number of Patients	129	723	852
Interim Analysis OS A vs. C			
Number of Events	89	413	502
Weights	0.420	0.908	-
Final Analysis OS A vs. C			
Number of Events	104	563	667
Weights	0.394	0.919	-

ITT = intent-to-treat; OS = overall survival.
A = ARM A; B = Arm B; C = Arm C.
Table shows estimates based on enrollment rates, randomization ratio, median OS of 12 and 17.1 months in Arm A and Arm C, respectively, 5% drop-out annually.

OS Hazard Ratio Arm A vs. Arm C

The HR, λ_A/λ_C, where λ_A and λ_C represent the hazard of death in Arm A and Arm C, respectively, and the 95% CI will be determined using the same methods as described for PFS above.

Kaplan-Meier methodology will be used to construct survival curves for both treatment arms and to estimate median OS for both treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS.

The duration of survival follow-up will be summarized for all patients in the analysis using descriptive statistics (median, range). Duration of survival follow-up is defined as the survival time for all patients in the analysis (whether patient is alive or has died).

4.4.2.2 OS in Arm B vs. Arm C

The ITT population for Arm B versus Arm C does not include Stage 1 patients. Therefore, for the analyses of OS in Arm B versus Arm C, stratification factors will be those used for randomization in Stage 2. The values for the stratification factors will be obtained from those entered in the IxRS at the time of randomization. Treatment comparisons will be based on the stratified log-rank test. Otherwise, the same methods will be used as for analyses of OS in Arm A versus Arm C.

For the primary analysis of OS in the ITT population for Arm B versus Arm C, all available data for these patients (before and after implementation of the iDMC recommendation in Protocol WO30070 v6) will be included.

The duration of follow-up in this population will be summarized as described above in Section 4.4.2.1.

4.4.2.3 OS in the PD-L1 IC2/3 Population

The analysis of OS in the PD-L1 IC2/3 population for Arm B versus Arm C will use the same methods as that for the ITT population for Arm B versus Arm C, except that PD-L1 status will not be one of the stratification factors. The analysis will include all available data for these patients (before and after implementation of the iDMC recommendation in Protocol WO30070 v6).

The duration of follow-up in this population will be summarized as described above in Section 4.4.2.1.

4.4.3 Secondary Efficacy Endpoints

4.4.3.1 Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients with a confirmed objective response, either CR or partial response (PR), observed on two consecutive assessments ≥ 28 days apart with the use of RECIST v1.1, based on investigator assessment. Patients without any post-baseline tumor assessments will be considered non-responders. The analysis population for ORR will be all randomized patients with measurable disease at baseline.

ORR will be compared between treatment arms (A vs. C and B vs. C) using the stratified Cochran Mantel-Haenszel test. The 95% CI for the difference in ORRs between the two treatment arms will be computed using the normal approximation to the binomial distribution. An estimate of ORR and its 95% CI will be calculated for each treatment arm using the Clopper-Pearson method.

In order to characterize responders, descriptive statistics (e.g., median, range) will be provided for time from randomization to response for patients with an objective response.

4.4.3.2 Duration of Response

DOR is defined, for patients with a confirmed objective response, as the time from the first documented objective response to documented disease progression with the use of RECIST v1.1, as determined by the investigator, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment at which they were known to be progression free. Because the determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing will not be performed.

Median DOR and corresponding 95% CIs will be estimated using Kaplan-Meier methodology for each treatment arm.

4.4.3.3 IRF-assessed PFS Arm A vs. Arm C

IRF-PFS is defined as the time from randomization to the first documented disease progression as assessed by an IRF using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment. Data for patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

As for investigator-assessed (INV)-PFS, an analysis of IRF-PFS will also be performed with the additional censoring rule for missed visits (see Section 4.4.1). Data for patients with an IRF-PFS event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.

The same methods as described above for INV-PFS will be used to determine the HR and 95% CI, median duration of IRF-PFS and 95% CI, and Kaplan Meier plots.

Analyses will be performed to evaluate the concordance between the two methods in patients who have a post-baseline assessment by both investigator as well as by IRF.

Sensitivity analyses for IRF-PFS are described in Section 4.4.5.1.

4.4.3.4 Timepoint Analysis of Progression-free Survival

The INV-PFS and IRF-PFS rates at 6 month intervals (e.g., 6 months, 1 year, etc.) in Arms A and C will be estimated by use of Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated by use of the standard error derived from Greenwood's formula. The 95% CI for the difference in PFS rates between Arms A and C will be estimated by use of the normal approximation method.

4.4.3.5 Timepoint Analysis of Overall Survival

The OS rates at 1, 2, and 3 years will be estimated by use of Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated by use of the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between Arms A and C or Arms B and C, respectively, will be estimated by use of the normal approximation method.

4.4.3.6 PFS in Arm B vs. Arm C

The HR for INV-PFS and IRF-PFS in the ITT population for Arm B versus Arm C and 95% CI will be estimated using a stratified Cox regression model with the stratification factors used for randomization in Stage 2.

Kaplan-Meier methodology will be used to construct PFS-event-free curves for both treatment arms and to estimate median PFS for both treatment arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS.

4.4.3.7 Patient-reported Outcomes

The European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) data will be scored according to the EORTC scoring manual (Fayers 2001). For all questionnaire subscales, if more than 50% of the constituent items are completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

Completion analysis will be performed in the ITT population for the overall EORTC QLQ-C30 questionnaire. Completion rates will be summarized by number and proportion of patients among those expected to complete the QLQ-C30 at each time point.

Time to deterioration in global health status in the ITT population will be compared between treatment groups (Arm A vs. Arm C and Arm B vs. Arm C) as a secondary efficacy endpoint with use of the log rank test (descriptive, two-sided). Deterioration in global health status is defined as a change from baseline of at least 10-points. Data for patients without a post-baseline assessment will be censored at the date of randomization plus 1 day. The HR will be estimated using a stratified Cox proportional hazards model and its 95% CI will be provided. The stratification factors will be the same as those used for the OS analysis comparing Arm A versus Arm C (pooled Stage 1 and Stage 2) and Arm B versus Arm C, respectively (see Section 4.4.2).

Kaplan-Meier methodology will be used to estimate the median time to deterioration in health status, and Kaplan-Meier curves will be produced.

Time to deterioration of the physical function score on the EORTC QLQ-C30 will be analyzed in the ITT population using the same methodology as for time to deterioration in global health status. Deterioration in physical function score is defined as a change from baseline of at least 10 points.

4.4.4 Exploratory Efficacy Endpoints

4.4.4.1 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients with either confirmed objective response (CR or PR), or stable disease (SD) maintained for $\geq$6 months, as determined by the investigator on the basis of RECIST v1.1. The analysis methods for DCR will be the same as those for ORR.

4.4.4.2 Biomarker Analyses

Per protocol, the exploratory biomarker objectives of the study are to investigate:

- Relationship between tumor tissue PD-L1 expression and measures of efficacy
- Predictive, prognostic, and pharmacodynamics (PD) exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment.

Exploratory biomarker analyses will be performed to examine the relationship between tumor tissue PD-L1 expression and measures of efficacy.

Additionally, predictive, prognostic and pharmacodynamics exploratory biomarkers in archival and/or fresh tumor tissue and/or blood will be examined for their association with disease status and/or clinical outcomes.

The tumor biomarkers include but are not limited to tissue tumor mutational burden (tTMB) using the cut-offs of ≥ 10 mutations/MB and ≥ 16 mutations/MB separately (given data availability), CD103, and CD8, as defined by IHC, quantitative reverse transcriptase−polymerase chain reaction (qRT−PCR), or other methods. Additional PD analyses of predictive, prognostic, and exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status, mechanisms of resistance, and/or response to study treatment will be conducted as appropriate. These exploratory analyses may be provided in a separate report.

4.4.4.3 QLQ-C30 Function Scores

Disease and treatment burden as measured by global health status, physical function, and other EORTC QLQ-C30 scales will be analyzed in the PRO-evaluable population. Data will be summarized descriptively as absolute mean scores and for single scores as percent of patients per category at each timepoint and at time to treatment discontinuation due to adverse events, clinical progression and radiographic progression (per protocol definition).

The number and proportion of patients with a clinically meaningful change, defined as a ≥ 10-point change of the score, for global health status and physical function will be summarized by treatment arm at each timepoint and at time to treatment discontinuation due to adverse events, clinical progression and radiographic progression (per protocol definition). The 95% CI around the proportion will be calculated using the Clopper-Pearson method for each treatment arm.

Repeated measures mixed-effects model will be used for comparing the global health status and physical function scores between treatment arms. The model will include a term for intercept, a term for linear time trend, a term for treatment group, and a term for treatment-by-time interaction. Time points following treatment discontinuation for any reason at the patient level or timepoints with less than 20% patients who completed these scales, where all subsequent time points also have less than 20% completion will be excluded.

4.4.5 Sensitivity Analyses

4.4.5.1 Analysis of PFS Accounting for Non-Protocol Anti-Cancer Therapy

The impact of non-protocol anti-cancer therapy on INV-PFS and IRF-PFS (Arms A vs. C) will be assessed depending on the number of patients who receive non-protocol therapy

before a PFS event. If > 5% of patients received non-protocol therapy before a PFS event in Arms A or C, a sensitivity analysis will be performed for the comparisons between treatment arms in which patients who receive non-protocol therapy before a PFS event will be censored at the last tumor assessment date before receipt of non-protocol therapy.

4.4.5.2 Analysis of OS Accounting for Non-Protocol Anti-Cancer Therapy

The impact of subsequent non-protocol anti-cancer therapy on OS (Arms A vs. C and Arms B vs. C) will be assessed depending on the number of patients who receive non-protocol anti-cancer therapy. If more than 10% of patients in the control arm have received a non-protocol anti-cancer (immune-) therapy that is considered to have an effect on their OS, the following analyses may be performed to compare treatment arms:

- OS in patients who switched will be discounted according to a range of possible effects on OS of subsequent non-protocol therapy.
- Additional sensitivity analyses may be conducted if deemed necessary.

4.4.5.3 Analysis of OS in Arm B vs. Arm C Accounting for Treatment Changes after Protocol Version 6

All patients in Arm B who were being treated with open-label atezolizumab monotherapy at the time of approval of Protocol v6 had the option of requesting unblinding of their PD-L1 status (see Section 2.2). If they were IC0 or 1, then a treatment alternative of atezolizumab plus platinum (cisplatin or carboplatin) and gemcitabine chemotherapy was provided if this was considered in the patient's best interest.

If a substantial number of such treatment switches occurred, additional sensitivity analyses may be performed to account for this using the same approach as described in Section 4.4.5.2.

A sensitivity analysis will also be performed on patients randomized to Arm B or Arm C prior to implementation of Protocol v6 that will include their data only up to the time of implementation of the iDMC recommendation.

4.4.5.4 Analyses of Impact of Loss to Follow-Up on OS

The impact of loss to follow-up on OS will be assessed depending on the number of patients who are lost to follow-up. For each comparison (Arms A vs. C; Arms B vs. C), if > 5% of patients are lost to follow-up for OS in any treatment arm, a sensitivity analysis will be performed for the comparisons between treatment arms in which patients who are lost to follow-up will be considered as having died at the last date they were known to be alive.

4.4.6 Subgroup Analyses

4.4.6.1 Subgroup Analyses of PFS and OS

Subgroup analyses will assess the consistency of the study results for the duration of INV-PFS (Arms A vs. C) and OS (Arms A vs. C and Arms B vs. C) across subgroups of the ITT populations. Subgroups will be defined by

- Demographics (e.g., age, sex, and race/ethnicity)
- Baseline characteristics, e.g.,
  - ECOG performance status
  - Time from prior chemotherapy
- Stratification factors:
  - Bajorin model risk factor score/liver metastasis
  - Investigator choice of chemotherapy
  - PD-L1 IHC IC status
- Enrollment stage

Summaries of INV-PFS and OS, including HRs estimated from Cox proportional hazards models and Kaplan-Meier estimates of median INV-PFS and OS, will be produced separately for each level of the categorical variables and displayed in a Forest plot.

Analyses including Stage 1 and 2 data will be stratified by enrollment stage. Analyses including only one enrollment stage will be unstratified.

Kaplan-Meier plots will be produced for selected subgroups.

Additional subgroup analyses may be conducted as appropriate.

4.4.6.2 Subgroup Analyses by Cisplatin-eligibility and Choice of Platinum Therapy

The determination of cisplatin eligibility of patients was to be made prior to randomization according to the Galsky criteria as defined in Protocol Section 4.2. Patients who met at least one of the following criteria were considered ineligible for cisplatin and should be treated with carboplatin plus gemcitabine if randomized to Arm A or Arm C; however, the final decision was made by the investigator:

- Impaired renal function (GFR $>$ 30 but $<$ 60 mL/min); GFR was to be assessed by direct measurement (i.e., creatinine clearance or ethyldediaminetetra-acetate) or, if not available, by calculation from serum/plasma creatinine (Cockcroft-Gault formula)
- NCI CTCAE v4.0 Grade $\geq$ 2 audiometric hearing loss of 25 decibels at two contiguous frequencies
- NCI CTCAE v4.0 Grade $\geq$ 2 peripheral neuropathy (i.e., sensory alteration or paresthesia, including tingling)
- ECOG performance status of 2

During the study, patients were allowed to switch from cisplatin to carboplatin chemotherapy if they became ineligible for cisplatin due to toxicity, or from carboplatin to cisplatin chemotherapy in the event that patient became eligible to receive cisplatin.

Subgroups will be defined based on cisplatin-eligibility per Galsky criteria and actual investigator choice of chemotherapy. Summaries will be provided by subgroup in the ITT populations for comparisons of Arm A versus Arm C and Arm B versus Arm C, including key demographic and baseline characteristics. Data on patients switching from cisplatin to carboplatin or vice versa will also be summarized.

Efficacy analyses, including of INV-PFS (Arm A vs. Arm C) and OS (Arm A vs. Arm C and Arm B vs. Arm C) will be performed in these subgroups using the same methods as those described in Section 4.4.6.1. Because these analyses will be based on a non-randomized subset of patients, formal hypothesis testing will not be performed.

4.4.6.3 Subgroup Analysis in Patients with a PD-L1 status of IC0 or IC1 Randomized to Arm B after Protocol Version 6

Efficacy data for patients with a PD-L1 status of IC0 or IC1 randomized to Arm B after implementation of the iDMC recommendation in Protocol WO30070 v6 will not be included in any formal efficacy analyses. Since this subgroup includes < 10 patients, descriptive listings will be provided.

4.5 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, SDs, and %CV, as appropriate. Additional PK analyses may be conducted if deemed appropriate.

4.6 SAFETY ANALYSES

Unless specified otherwise, safety analyses described below will be conducted for the safety population (see Section 4.1.6). The safety-evaluable population is defined as patients who received any amount of any component of the study treatments. Patients will be analyzed according to the treatment received. In particular, patients randomized to the monotherapy arm after approval of Protocol WO30070 v6, who received combination open-label atezolizumab and chemotherapy will be pooled with patients in Arm A for safety analyses. For the analyses of safety, data from patients enrolled before and after Protocol WO30070 v3, will be pooled by treatment arm.

4.6.1 Exposure to Study Medication

Study drug exposure, including treatment duration, number of cycles, and dose intensity, will be summarized for each treatment arm and for each study drug with descriptive statistics.

4.6.2 Adverse Events

Verbatim description of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. AEs will be graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0. Treatment-emergent AEs will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade and treatment arm. Multiple occurrences of the same event will be counted once at the maximum grade. All reported AEs, SAEs, Grade 5 AEs, treatment-related AEs (as assessed by the investigator), severe AEs (Grade $\geq$ 3), adverse events of special interest (AESIs), AEs leading to study drug discontinuation, and AEs leading to interruption or reduction will be summarized.

All listings of AEs will include all AEs with onset on or after the first study drug treatment up to the data cut-off date.

All deaths and causes of death will be summarized by treatment arm overall as well as, during the study treatment period and those reported during the follow-up period after treatment discontinuation.

4.6.3 Laboratory Data

Laboratory data will be summarized by treatment arm. Laboratory data will be graded according to NCI CTCAE and will be summarized descriptively with shift tables from baseline to worst value post-baseline.

4.6.4 Vital Signs

Changes from baseline in selected vital signs will be summarized by treatment arm. ECOG performance status will also be summarized over time.

4.6.5 Anti-Therapeutic Antibodies

Incidence of anti-therapeutic antibodies (ATAs) against atezolizumab will be summarized. The analyses of pharmacokinetics, key efficacy, and safety by ATA status may be conducted to explore the potential impact of immunogenicity.

4.6.6 Subgroup Analyses

Analyses of safety in selected subgroups, e.g., by cisplatin-eligibility and investigator choice of chemotherapy (see Section 4.4.6.2), will be provided.

5. REFERENCES

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Appendix 1 Protocol Synopsis

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) AS MONOTHERAPY AND IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC UROTHELIAL CARCINOMA**
PROTOCOL NUMBER:	WO30070
VERSION NUMBER:	8
EUDRACT NUMBER:	2016-000250-35
IND NUMBER:	120827
TEST PRODUCT:	Atezolizumab (RO5541267), gemcitabine, carboplatin, cisplatin
PHASE:	Phase III
INDICATION:	Urothelial cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This is a Phase III, multicenter, randomized, placebo-controlled, partially blind study designed to evaluate the efficacy of atezolizumab given as monotherapy or in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy.

Efficacy Objectives

The primary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy on the basis of the following endpoints:

- Co-primary endpoints of progression-free survival (PFS) and overall survival (OS)

  PFS is defined as the time from randomization to the first documented disease progression as determined by the investigator with use of Response Evaluation Criteria in Solid Tumors Version 1 (RECIST v1.1), or death due to any cause, whichever occurs first.

  OS is defined as the time from randomization to death due to any cause.

In addition, a primary efficacy objective is to evaluate the efficacy of atezolizumab monotherapy compared with placebo plus platinum-based chemotherapy on the basis of OS, as defined above.

The secondary efficacy objectives for this study are to evaluate the efficacy of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo in combination with platinum-based chemotherapy on the basis of the following endpoints:

- Objective response rate (ORR), defined as the proportion of patients with a confirmed objective response, either complete response (CR) or partial response (PR), observed on two assessments ≥28 days apart per RECIST v1.1, based on investigator assessment
- Duration of response (DOR), defined for patients with an objective response as the time from the first documented objective response to documented disease progression per RECIST v1.1, based on investigator assessment, or death due to any cause, whichever occurs first
- IRF-PFS, defined as the time from randomization to the first documented disease progression as determined by blinded independent central review with use of RECIST v1.1, or death due to any cause, whichever occurs first
- Investigator-assessed (INV-PFS) in patients treated with atezolizumab monotherapy compared with patients treated with placebo plus platinum-based chemotherapy
- OS rate at 1 year
- PFS rate at 1 year
- Time to deterioration in global health status as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30)
- Time to deterioration in physical function as measured by the EORTC QLQ-C30

Exploratory Efficacy Objectives

The exploratory efficacy objectives for this study are to evaluate the efficacy of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo in combination with platinum-based chemotherapy on the basis of the following endpoints:

- Disease control rate (DCR), defined as the proportion of patients with confirmed CR or PR as best response, or stable disease maintained for ≥ 6 months, per RECIST v1.1
- Relationship between tumor tissue programmed death–ligand 1 (PD-L1) expression and measures of efficacy
- Predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment
- Disease and treatment burden as measured by the symptom (e.g., pain, fatigue) and function scores from the QLQ-C30

An additional exploratory objective is to characterize patients who are able to continue treatment past progression by RECIST v1.1 as permitted per protocol and to describe clinical outcomes by treatment arm using modified RECIST, such as ORR, DOR, DCR, and PFS.

Health Economics Objective

Health status will be measured using the EuroQol 5-Dimension, 5-Level version (EQ-5D-5L) questionnaire to be included in health economic modeling. As such, data from the EQ-ED-5L will not be reported in the Clinical Study Report.

Safety Objectives

The safety objectives for this study are to evaluate the safety and tolerability of atezolizumab given as either monotherapy or in combination with platinum-based chemotherapy compared with placebo plus platinum-based chemotherapy on the basis of the following:

- Incidence, nature, and severity of adverse events graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0
- Changes in vital signs, and clinical laboratory results

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the pharmacokinetics of atezolizumab when administered as monotherapy or in combination with platinum-based chemotherapy in patients who are treatment-naive:

- PK parameters for atezolizumab include maximum serum concentration and minimum serum concentration when appropriate, as data allow.

Immunogenicity Objective

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab as monotherapy and in combination with platinum-based chemotherapy on the basis of the following endpoint:

- Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline

The exploratory immunogenicity objective for this study is to evaluate potential effects of detectable ATAs on the basis of the following endpoint:

- Correlation between ATA status and efficacy, safety, and PK endpoints

Study Design

Description of Study

This is a Phase III, multicenter, randomized, placebo-controlled, partially blind study (IMvigor130) designed to evaluate the safety and efficacy of atezolizumab given as monotherapy or in combination with platinum-based chemotherapy versus placebo in combination with platinum-based chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who have not received prior systemic therapy.

Treatment with platinum-based chemotherapy can continue until progressive disease (PD) per RECIST v1.1 or unacceptable toxicity per investigator discretion. In the case of CR, only two more cycles of platinum-based chemotherapy will be administered after the response confirmation. In specific circumstances, treatment may continue beyond disease progression.

No crossover will be allowed from the control arm to either experimental arm (Arms A and B).

Patients should be considered eligible to receive treatment with platinum-based chemotherapy (either gemcitabine with cisplatin or gemcitabine with carboplatin) and have measurable disease, defined by RECIST v1.1.

Note, the study was initially implemented with randomization to two treatment arms (carboplatin plus gemcitabine with or without atezolizumab) in patients who were ineligible for cisplatin-based chemotherapy. In Protocol WO30070, Version 3, a third treatment arm was added (open-label atezolizumab monotherapy). In addition, the eligibility criteria were expanded to also allow patients who are eligible for cisplatin-based chemotherapy to enter the study. Protocol WO30070, Version 3 was implemented while recruitment was ongoing. Patients recruited into the study prior to Version 3 will be included in the final analysis.

Tumor specimens from eligible patients will be prospectively tested for PD-L1 immunohistochemistry (IHC) expression by a central laboratory prior to randomization. The IHC scores will have three categories (tumor-infiltrating immune cell [IC]0, IC1, IC2/3). Sponsor, patients, and investigators will be blinded to the PD-L1 expression status, but the Sponsor will be able to view aggregate PD-L1 expression data. An exception is the case for any new patients enrolled in Arm B, in which PD-L1 status will be unblinded to the patient and investigator at the time of randomization. However, the Sponsor will not be able to review these scores (see below for further information regarding Protocol Version 6 update based on iDMC recommendation). The study will enroll all eligible patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status.

This study will enroll approximately 1200 patients at approximately 229 sites globally.

Following implementation of Protocol WO30070, Version 3, patients will be randomized in a 1:1:1 ratio to receive one of the following:

- Arm A (experimental arm): blinded atezolizumab in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)

- Arm B (experimental arm): open-label atezolizumab monotherapy
- Arm C (control arm): blinded placebo in combination with open-label platinum-based chemotherapy (gemcitabine with either cisplatin or carboplatin)

Based on an ad-hoc review of survival data of all patients randomized in the study up to 12 March 2018, the study iDMC recommended closure of Arm B (atezolizumab monotherapy) to further accrual of all patients with a PD-L1 expression status of IC0 or IC1. The iDMC did not recommend a change in therapy for patients already randomized to monotherapy on study.

The iDMC recommendation also stated that patients with a PD-L1 expression status of IC2/3 can continue to be randomized to Arm A, B, or C and that Arms A and C should remain unchanged (open to all patients regardless of PD-L1 status).

Randomization to the three arms in a 1:1:1 ratio will continue regardless of PD-L1 status.

Prior to randomization, all patients will be informed per the consent form that if randomized to Arm B (atezolizumab monotherapy) and are determined to have a tumor PD-L1 expression status of IC0 or IC1, they will receive chemotherapy combined with atezolizumab instead of atezolizumab monotherapy. The consent will also inform patients who are randomized to Arm B, are found to have with a tumor PD-L1 expression status of IC0 or IC1, and who are not willing to undergo treatment with atezolizumab with chemotherapy should consider treatment outside of the trial rather than proceeding with trial enrollment.

<u>For all new patients randomized to Arm B (open-label atezolizumab monotherapy) after approval of Protocol WO30070, Version 6:</u>

- The PD-L1 status will be unblinded to the investigator and patient at the time of randomization.
- Patients whose PD-L1 expression status of IC2/3 will receive atezolizumab monotherapy.
- Patients with a PD-L1 expression status of IC0 or IC1 will receive open-label atezolizumab plus platinum (carboplatin or cisplatin) and gemcitabine chemotherapy instead of atezolizumab monotherapy.

  If a patient with a PD-L1 expression status of IC0 or IC1 subsequently wished to receive standard-of-care chemotherapy instead of atezolizumab plus platinum and gemcitabine chemotherapy will be able to receive standard-of-care chemotherapy of their choice (to be provided outside of the protocol) and continue on survival follow up.

<u>For all patients in Arm B who are currently being treated with open-label atezolizumab monotherapy at the time of approval of Protocol WO30070, Version 6:</u>

- Patients will be informed that the iDMC has not recommended any changes to therapy for those already randomized to atezolizumab monotherapy.
- PD-L1 status may be unblinded to the patient and the investigator upon request.
- Patients with PD-L1 expression status of IC2/3 will continue receiving atezolizumab monotherapy.
- Patients with PD-L1 expression status of IC0 or IC1 are recommended to continue with atezolizumab monotherapy, as the iDMC did not recommend a change in therapy for patients already randomized to monotherapy on study.

  However, if the patient after discussion of benefit-risk with the treating physician determines that continuation of atezolizumab monotherapy is not considered beneficial, a treatment alternative of atezolizumab plus platinum (cisplatin or carboplatin) and gemcitabine chemotherapy will be provided. These patients should then be treated the same as patients in Arms A and C.

  If the decision is made to unblind the patient and add platinum (cisplatin or carboplatin) and gemcitabine chemotherapy to the regimen, it must be added before the patient has known progressive disease. Chemotherapy cannot be added to patients in Arm B with documented progressive disease within the study.
- Patients will also have the option to stop study therapy and receive standard-of-care treatment outside of the study by their physician.

- All patients (including those who choose to stop atezolizumab monotherapy) are requested to continue in the study for survival follow up.

Prior to randomization, the investigator will select which chemotherapy the patient should receive (gemcitabine and carboplatin vs. gemcitabine and cisplatin) if the patient is randomized to Arm A or Arm C. The Galsky criteria should be used to guide determination of cisplatin ineligibility. The criteria to determine ineligibility for cisplatin should be the same as the criteria used in the initial implementation of the study.

Randomization will be stratified by the following factors:

- PD-L1 status (IC0 vs. IC1 vs. IC2/3)
- Bajorin model risk factor score/liver metastasis (0 vs. 1 vs. 2 or patients with liver metastasis)
- Investigator-determined chemotherapy (gemcitabine and carboplatin vs. gemcitabine and cisplatin)

Gemcitabine will be administered at a dose of 1000 mg/m^2 by intravenous (IV) infusion on Day 1 and Day 8 of each 21-day cycle.

Carboplatin will be administered at area under the concentration–time curve (AUC) 4.5 by IV infusion on Day 1 of each 21-day cycle.

Cisplatin will be administered at a dose of 70 mg/m^2 by IV infusion on Day 1 of each 21-day cycle. Split dosing of cisplatin is not permitted.

All visits and infusions may be administered with a window of $\pm$ 3 days, except for the Day 8 visit. The Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (-1 to $+3$) of a cycle.

Gemcitabine and platinum chemotherapy (carboplatin or cisplatin) will be administered until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

For patients who receive chemotherapy and who have a CR, only two more cycles of chemotherapy will be administered after the response confirmation.

For patients who receive chemotherapy and who have a PR or stable disease, chemotherapy administration may be discontinued after completion of six cycles, if necessary, to comply with institutional guidelines.

If the initial protocol doses of chemotherapy agents differ from institutional guidelines or local label, the initial doses may be modified to achieve compliance.

Atezolizumab will be administered at a fixed dose of 1200 mg by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1.

Placebo for atezolizumab (Arm C) will be administered by IV infusion on Day 1 of each 21-day cycle until investigator-assessed disease progression per RECIST v1.1. In specific circumstances, treatment may continue beyond disease progression. No crossover will be allowed from the control arm to either experimental arm (Arms A and B).

Patients will undergo scheduled tumor assessment at baseline and every 9 weeks (from initiation of the first dose) thereafter for 54 weeks after randomization. After 54 weeks, patients will undergo tumor assessment every 12 weeks until disease progression per RECIST v1.1, death, study termination by the Sponsor, or withdrawal of consent, whichever occurs first. Patients must discontinue treatment at the first occurrence of radiographic progression, per RECIST v1.1, with the following exception: Patients who have achieved a PR or CR of target lesions and who develop new lesions (≤ 3) that are amenable to surgery or ablative techniques (e.g., radiotherapy, radiofrequency ablation) may continue to receive study treatment if they demonstrate no further progression of disease at the next imaging assessment and continue to demonstrate clinical benefit per investigator. Because gemcitabine is not indicated for use in combination with radiation therapy and has been shown to cause excess toxicity (mucositis, pneumonitis) as well as radiation recall when administered in close proximity to radiation therapy, patients who continue treatment with gemcitabine should not receive radiation to ports that include a significant proportion of lung or mucosal surface (esophagus, intestine). In the absence of disease progression, tumor assessments should continue, regardless of whether

patients start new anti-cancer therapy, until death, loss of follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. Follow-up data capture, including subsequent anti-cancer therapies (including targeted therapies and immunotherapies), will continue for each patient until death, loss of follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients are required to undergo tumor biopsy sample collection, if clinically feasible as assessed by investigators, at the first evidence of radiographic disease progression. These data will be used to confirm that radiographic findings are consistent with the presence of tumor. In addition, these data will be analyzed for the association between changes in tumor tissue and clinical outcome and to understand further the potential mechanisms of resistance to treatment.

All primary imaging data used for tumor assessment will be collected by the Sponsor to enable a centralized independent review.

Safety assessments will include the incidence, nature, and severity of adverse events, vital signs and laboratory abnormalities graded per the NCI CTCAE v4.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient samples, including archival tumor tissues, as well as serum, plasma, and blood, will be collected for future exploratory biomarker assessments.

An external independent Data Monitoring Committee (iDMC) will evaluate safety data according to policies and procedures detailed in an iDMC Charter.

After approximately 1200 patients have been randomized, enrollment in sites will be closed.

Number of Patients

Approximately 229 sites globally will participate in the study, and approximately 1200 patients will be randomized.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age $\geq$ 18 years
- Considered to be eligible to receive platinum-based chemotherapy, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$ 2
- Able to comply with the study protocol, in the investigator's judgment
- Histologically documented, locally advanced (T4b, any N; or any T, N 2–3) or metastatic urothelial carcinoma (M1, Stage IV) (also termed TCC or UCC of the urinary tract; including renal pelvis, ureters, urinary bladder, and urethra)

  Patients with mixed histologies are required to have a dominant transitional cell pattern.

  Locally advanced bladder cancer must be inoperable on the basis of involvement of pelvic sidewall or adjacent viscera (clinical Stage T4b) or bulky nodal metastasis (N2–N3).
- Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks preferred) or at least 15 unstained slides, with an associated pathology report, for central testing and determined to be evaluable for tumor PD-L1 expression prior to study enrollment; patients who have fewer than 15 unstained slides available at baseline (but no fewer than 10) may be eligible following discussion with the Medical Monitor.

  Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation.

  Transurethral Resection of Bladder Tumor (TURBT) specimens must contain a muscle invasive component (i.e., T2 or greater) of the bladder tumor as verified by local pathology review. If the TURBT specimens do not contain a muscle invasive

component, then specimens obtained at the time of cystectomy/nephroureterectomy (i.e., pT2 or greater) or metastatic spread (i.e., sample from a metastatic lesion) will be required prior to randomization. An archival specimen, if available, should also be submitted.

Patients who do not have tissue specimens that meet eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.

Patients who have additional tissue samples from procedures performed at different times during the course of their urothelial carcinoma may also submit these samples for central testing. Tissue samples that are obtained at multiple times for individual patients may contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anti-cancer therapy. In situations where multiple specimens were received from different sites or at different times, the highest score will be used for stratification and for subsequent analyses.

- No prior chemotherapy for inoperable, locally advanced, or metastatic urothelial carcinoma

  For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval > 12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment naive in the metastatic setting.

  Prior local intravesical chemotherapy or immunotherapy is allowed if completed at least 4 weeks prior to the initiation of study treatment.
- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions should not be counted as target lesions unless there has been demonstrated progression in the lesion since radiotherapy and no other lesions are available for selection as target lesions.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 days prior to the first study treatment:

  ANC ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)

  WBC counts > 2500 cells/μL

  Lymphocyte count ≥ 300 cells/μL

  Platelet count $\geq 100{,}000$ cells/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)

  Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused to meet this criterion.

    Patients with a solitary kidney or chronic kidney disease with low erythropoietin production may use erythropoietin-stimulating agents.

  AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ the upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases: alkaline phosphatase $\leq 5 \times$ ULN

  Serum bilirubin $\leq 1.5 \times$ ULN

    Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled.

PTT/aPTT $\leq 1.5 \times$ ULN

PT $\leq 1.5 \times$ ULN or INR < 1.7

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

Calculated creatinine clearance ≥ 30 mL/min (Cockcroft-Gault formula)

Serum calcium ≤ 3 mmol/L

For patients with serum albumin < 40 g/L, corrected serum calcium must be $\leq$ ULN

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 6 months after the last dose of carboplatin, cisplatin, or gemcitabine or for 5 months after the last dose of atezolizumab

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established and proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 6 months after the last dose of gemcitabine and/or carboplatin, and/or cisplatin. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

<u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

Cancer-Specific Exclusions

- Any approved anti-cancer therapy, including chemotherapy or hormonal therapy, within 3 weeks prior to initiation of study treatment; the following exceptions are allowed:

  Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging.

  Hormone-replacement therapy or oral contraceptives
- Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 28 days prior to enrollment
- Active or untreated CNS metastases as determined by computed tomography (CT) or magnetic resonance imaging evaluation during screening and prior radiographic assessments

  Patients with treated asymptomatic CNS metastases are eligible, provided they meet all of the following criteria:

  Evaluable or measurable disease outside the CNS

No metastases to midbrain, pons, medulla, or within 10 mm of the optic apparatus (optic nerves and chiasm)

No history of intracranial or spinal cord hemorrhage

No ongoing requirement for corticosteroid as therapy for CNS disease; anti-convulsants at a stable dose are allowed

No evidence of significant vasogenic edema

No stereotactic radiation, whole-brain radiation or neurosurgical resection within 4 weeks prior to Cycle 1, Day 1

Radiographic demonstration of interim stability (i.e., no progression) between the completion of CNS-directed therapy and the screening radiographic study

Screening CNS radiographic study ≥ 4 weeks since completion of radiotherapy or surgical resection and ≥ 2 weeks since discontinuation of corticosteroids

- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled tumor-related pain

  Patients who require pain medication must be on a stable regimen at study entry.

  Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to enrollment.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
- Uncontrolled hypercalcemia defined as any one or more of the following criteria:

  > 1.5 mmol/L ionized calcium

  Serum calcium > 3 mmol/L

  Corrected serum calcium $>$ ULN (if serum albumin < 40 g/L)

  Symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab

  Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Malignancies other than urothelial carcinoma within 5 years prior to Cycle 1, Day 1

  Patients with localized prostate cancer (defined as Stage $\leq$ pT2c, Gleason score ≤ 7, and prostate-specific antigen (PSA) at prostate cancer diagnosis ≤ 20 ng/mL) treated with curative intent and without PSA recurrence are eligible.

  Patients with pre-existing low-risk prostate cancer (defined as Stage cT1/T2a, Gleason score ≤ 6 and PSA ≤ 10 ng/mL) who are treatment-naive and undergoing active surveillance are eligible.

  Patients with malignancies of a negligible risk of metastasis or death (e.g., risk of metastasis or death $< 5\%$ at 5 years) are eligible provided they meet all of the following criteria:

  Malignancy treated with expected curative intent (e.g., adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent)

  No evidence of recurrence or metastasis by follow-up imaging and any disease-specific tumor markers

General Medical Exclusions

- Life expectancy of < 12 weeks
- Pregnant or lactating, or intending to become pregnant during the study

  Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
- Serum albumin < 25 g/L

Exclusion Criteria Related to Atezolizumab

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for this study.

  Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis) are permitted provided that they meet the following conditions:

  Rash must cover less than 10% of body surface area (BSA)

  Disease is well controlled at baseline and only requiring low potency topical steroids

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- Patients with prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class III or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina
- Known left ventricular ejection fraction (LVEF) $< 40\%$

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF 40%–50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. Patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary disease, congestive heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram.
- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. A negative HBV DNA test must be obtained in these patients prior to Cycle 1, Day 1.

Patients who test positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

- Active tuberculosis
- Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Therapeutic oral or IV antibiotics within 2 weeks prior to randomization

  Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease or for dental extraction) are eligible.
- Major surgical procedure within 4 weeks prior to randomization or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis.
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1

  Influenza vaccination should be given during influenza season only (approximately October through May in the Northern Hemisphere and approximately April through September in the Southern Hemisphere).

  Patients must agree not to receive live, attenuated influenza vaccine within 28 days prior to initiation of study treatment, during treatment, or within 5 months after the last dose of atezolizumab.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Prior treatment with CD137 agonists, anti–CTLA-4, anti–programmed death-1 (PD-1), or anti–PD-L1 therapeutic antibody or pathway-targeting agents
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to Cycle 1, Day 1.
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) within 2 weeks prior to Cycle 1, Day 1 or anticipated requirement for systemic immunosuppressive medications during the study

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.

  The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed.

End of Study

The end of this study is defined as the date when the required number of deaths has been observed for the final analysis of OS in the global (main) study's intent-to-treat (ITT) population. Additionally, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the global (main) study, from randomization of the first patient to the end of the study, is expected to be approximately 44 months.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are atezolizumab, placebo, gemcitabine, carboplatin, and cisplatin.

Test Products (Investigational Drugs)

Atezolizumab

The dose level of atezolizumab in this study is 1200 mg administered by IV infusion every 3 weeks (q3w). Administration of atezolizumab and placebo will be performed in a setting with

emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Gemcitabine

Gemcitabine will be administered according to the local prescribing information. The starting dose of gemcitabine will be 1000 mg/m^2, administered by IV infusion on Day 1 and Day 8 of each 21-day cycle. The Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (-1 to $+3$) of a cycle. A change of body weight $\pm$ 5% compared to previous measured weight requires that the dose be re-calculated.

Carboplatin

Carboplatin will be administered according to the local prescribing information. The starting dose of carboplatin will be calculated to achieve an AUC of 4.5, administered by IV infusion on Day 1 of each 21-day cycle. If institutional guidelines conflict with protocol carboplatin dosing, carboplatin may be administered at a maximum starting AUC of 5.0. A change of body weight $\pm$ 5% compared to previous measured weight requires that the dose be re-calculated.

Cisplatin

Cisplatin will be administered according to the local prescribing information. The starting dose of cisplatin will be 70 mg/m^2, administered by IV infusion on Day 1 of each 21-day cycle. Split dosing of cisplatin is not permitted. A change of body weight $\pm$ 5% compared to previous measured weight requires that the dose be re-calculated.

Comparator

Placebo

The placebo will be identical in appearance to atezolizumab and comprise the same excipients but without atezolizumab drug product. It should be handled, stored, and used in the same manner as atezolizumab (by IV infusion q3w).

Duration of Chemotherapy Treatment

Gemcitabine and platinum chemotherapy (carboplatin or cisplatin) will be administered until investigator-assessed disease progression per RECIST v1.1 or unacceptable toxicity.

For patients in the combination arms who receive chemotherapy (Arms A and C) and who have a CR, only two more cycles of chemotherapy will be administered after the response confirmation.

For patients in the combination arms who receive chemotherapy and who have a PR or stable disease, chemotherapy administration may be discontinued after completion of six cycles, if necessary, to comply with institutional guidelines.

Non-Investigational Medicinal Products

None

Statistical Methods

Primary Analysis

The efficacy analyses for PFS and OS will be performed on all randomized patients (ITT population) for the respective treatment arm comparison according to the analysis hierarchy. Patients will be grouped according to the treatment assigned at randomization. Analysis of secondary and exploratory efficacy endpoints will be performed for randomized patients in the ITT population.

Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are PFS as assessed by the investigator using RECIST v1.1 and OS. Because type I error will be controlled accounting for two co-primary endpoints, the study will be considered a positive study if statistical significance is achieved for either of the co-primary endpoints.

PFS is defined as the time from randomization to the first documented disease progression as assessed by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment. Data for patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

For U.S. registration purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits.

OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The following analyses will be performed for both PFS and for OS. PFS and OS will be compared between treatment arms with the use of the stratified log-rank test. For the comparisons of Arm A versus Arm C, a possible effect of study stage will be taken into account.

The HR for PFS and OS will be estimated using a stratified Cox regression model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors, with values as recorded in the IxRS. Results from an unstratified analysis will also be presented. Kaplan-Meier methodology will be used to estimate median PFS and OS for each treatment arm, and Kaplan-Meier plots will be constructed to provide a visual description of the difference between the treatment and control arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm.

For the primary analysis of OS in the ITT population for Arm B versus Arm C, all available data for these patients (before and after implementation of the iDMC recommendation in Protocol WO30070, Version 6) will be included.

However, if a substantial number of patients with a PD-L1 expression status of IC0 or IC1 randomized to Arm B prior to implementation of Protocol WO30070, Version 6 choose to switch to the combination of atezolizumab and chemotherapy, an additional analysis may be performed to account for treatment switching. A sensitivity analysis will also be performed on patients randomized to Arm B or Arm C prior to implementation of Protocol WO30070, Version 6 that will include their data only up to the time of implementation of the iDMC recommendation.

The analysis of OS in the PD-L1 IC2/3 population for Arm B versus Arm C will use the same methods as that for the ITT population for Arm B versus Arm C, except that PD-L1 status will not be one of the stratification factors. The analysis will include all available data for these patients (before and after implementation of the iDMC recommendation of Protocol WO30070, Version 6).

Determination of Sample Size

A total of approximately 1200 patients will be randomized to the study (Stage 1 and Stage 2 combined).

Enrollment of approximately 1200 patients is based on the following assumptions: approximately 258 patients are projected to be enrolled in Stage 1 and allocated 2:1 to Arm A (atezolizumab in combination with platinum therapy) or Arm C (placebo in combination with platinum therapy). Approximately 942 patients are projected to be enrolled in Stage 2 and allocated 1:1:1 to Arm A, Arm B (atezolizumab monotherapy), or Arm C.

Simulations were performed to check the expected power of the analyses of co-primary endpoints PFS and OS for this sample size.

Interim Analyses

There are no interim analyses planned for PFS in this study.

A total of *three* efficacy analyses of OS are planned (*two* interim *analyses* and the final analysis). The final analysis of OS in Arm A versus Arm C will be performed when approximately 667 OS events in Arm A and Arm C of the ITT population have occurred. *Based on observed survival up to the final PFS/interim OS analysis, the required* number *of events* is projected to occur at Month *55 from the time* the first patient *was* randomized.

The interim and final analyses of OS in Arms A versus C and Arms B versus C will be performed according to the analysis hierarchy.

The *first* interim OS analysis will be conducted by the Sponsor at the time of the final PFS analysis.

The second interim OS analysis will take place after approximately *12 months of* additional *follow-up compared with* the *clinical cut-off date* for the *primary* analysis*, or when at least 579 patients (68%) have died* in Arm A *and* C*, whichever is later.*

Because the patient populations enrolled during Stage 1 and Stage 2 are considered independent, standard methods of group sequential designs apply.

If the required number of OS events in Arm B versus Arm C *has not been* reached at the time of the *second interim or final* OS analysis in Arm A versus Arm C, then *two further* interim analys*es* for the comparison of Arm B versus Arm C may be performed at the time of *these analyses.*

To control type I error for OS, the stopping boundaries for the OS interim and final analyses are to be computed for the appropriate alpha level with use of the Lan-DeMets implementation of the O'Brien-Fleming use function.

Appendix 2 Schedule of Assessments

Assessment Window (Days) [b]	Screening [a]		Treatment Cycles (Each cycle = 21 days)				Treat. Discon. (≤ 30 Days) [c]	90 Day Follow-Up	Survival Follow-Up [d]
			Platinum/Gem + Atezolizumab or Platinum/Gem + Placebo			Atezolizumab/ Placebo Monotherapy			
	–28 to –1	–7 to –1	Day 1	Day 8 [gg]	Day 15	Day 1			
Informed consent [a]	x								
Medical, surgical, and cancer histories, including demographic information [e]	x								x Cancer treatment
Age-adjusted Charlson comorbidity index	x								
HIV, HBV, HCV serology [f]	x								
TB test [g]	x								
Concomitant medications [h]	x		x			x	x	x	
Screening CT/MRI (chest/abdomen/pelvis/head) [i]	x								
Tumor assessment [j]	x		Every 9 weeks (±3 business days) for 54 weeks and every 12 weeks (±6 business days) thereafter until disease progression, death, or loss of follow-up						
Complete physical examination [k]	x						x		
Limited physical examination [l]			x [m]			x [m]		x	
ECOG performance status	x		x [m]			x [m]	x		
Vital signs [n]	x		x			x	x		
12-lead ECG [o]	x						x		

Appendix 2 Schedule of Assessments (cont.)

Assessment Window (Days) [b]	Screening [a]		Treatment Cycles (Each cycle = 21 days)				Treat. Discon. (≤ 30 Days) [c]	90 Day Follow-Up	Survival Follow-Up [d]
			Platinum/Gem + Atezolizumab or Platinum/Gem + Placebo			Atezolizumab/ Placebo Monotherapy			
	–28 to –1	–7 to –1	Day 1	Day 8[gg]	Day 15	Day 1			
Echocardiogram [o]	x								
Weight [p, q]	x		x				x		
Height	x								
Hematology [r]	x		x	x	x [r]	x	x	x	
Serum chemistry [s]	x		x			x	x	x	
Serum pregnancy test [t]		x	x [t]			x [t]	x [t]		
Coagulation panel (PTT/aPTT, INR)	x						x		
Urinalysis [u]	x		x			x	x	x	
TSH, free T3, free T4 [v]	x		x [v]			x [v]	x	x	
Serum ferritin	x		x [v]			x [v]	x	x	
Optional blood sample for RBR DNA [w]		x							
Blood samples for pharmacodynamics biomarkers [x]			x			x			
CRP		x [y]	x [k]			x [y]	x		
Autoantibody testing [y]	x					x	x		
Serum sample for PK sampling [z]			x			x	x		x [z]

Appendix 2 Schedule of Assessments (cont.)

Assessment Window (Days) [b]	Screening [a]		Treatment Cycles (Each cycle = 21 days)				Treat. Discon. (≤ 30 Days) [c]	90 Day Follow-Up	Survival Follow-Up [d]
			Platinum/Gem + Atezolizumab or Platinum/Gem + Placebo			Atezolizumab/ Placebo Monotherapy			
	–28 to –1	–7 to –1	Day 1	Day 8 [gg]	Day 15	Day 1			
Serum sample for ATA [aa]			x [aa]			x [aa]	x		x [aa]
Archival and/or fresh FFPE tumor tissue specimen or 15 unstained slides for eligibility [bb]	x								
PROs (EORTC QLQ-C30 and EQ-5D-5L) [cc]			x			x	x		x
Fresh biopsy at the time of radiographic progression [dd]			x						
Optional RBR tumor biopsy samples [ee]			x						
Atezolizumab/placebo infusion [ff]			x			x			
Gemcitabine infusion [p]			x	x					
Carboplatin or cisplatin infusion [q]			x						
Adverse events [gg]	x	x	x	x	x	x	x	x	x

Appendix 2 Schedule of Assessments (cont.)

anti-HBc = antibody against hepatitis B core antigen; ATA = anti-therapeutic antibody; AUC = area under the concentration–time curve; CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; ePRO = electronic patient-reported outcome; EQ-5D-5L = Euro QoL 5-Dimensions 5-Level; FFPE = formalin fixed paraffin embedded; Gem = gemcitabine; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; IGRA = interferon-gamma release assay; IV = intravenous; LVEF = left ventricular ejection fraction; PD = progressive disease; PD-L1 = programmed death-ligand 1; PK = pharmacokinetic; Platinum = cisplatin or carboplatin; PRO = patient-reported outcome; QLQ-C30 = Quality-of-life Questionnaire Core 30; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; TB = tuberculosis; TBNK = T, B, and natural killer; TSH = thyroid-stimulating hormone.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Written informed consent is required for performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry (except where otherwise specified) may be used for screening assessments rather than repeating such tests. If re-screening is required, then HBV, HCV, HIV, CRP, and autoantibody testing from the initial screening may be acceptable for screening assessment if performed $<$ 60 days from Cycle 1 Day 1.

[b] The first dosing day (Cycle 1, Day 1) should occur within 5 days from date of randomization. All visits and infusions may be administered with a window of $\pm$ 3 days, except for the Day 8 visit. Day 8 dose of gemcitabine may be given no earlier than Day 7 but may be given up to Day 11 (-1 to $+3$) of a cycle. Blood counts for gemcitabine dosing should be obtained within 1 day prior to Day 1 and Day 8 of each cycle of therapy.

[c] Patients will be asked to return to the clinic not more than 30 days after the last treatment for a treatment discontinuation visit.

[d] Starting from the treatment discontinuation visit, survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months ($\pm$ 30 days) until death, loss to follow-up, or study termination by the Sponsor. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[e] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes age, sex, and self-reported race/ethnicity. Reproductive status and smoking history should also be captured.

[f] All patients will be tested for HIV locally prior to the inclusion into the study, and HIV-positive patients will be excluded from the clinical study. HBsAg, anti-HBc antibody and anti-HBs antibody should be collected during screening and tested locally. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be collected and tested prior to Cycle 1, Day 1.

[g] All patients will have tuberculin (PPD) skin test or IGRA performed locally prior to inclusion into the study, and patients with active TB will be excluded from the clinical study.

[h] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has

used within the 7 days prior to initiation of study drug should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[i] All patients will have imaging during screening to establish measurable lesions per RECIST v1.1 Screening assessments must include CT scans (with oral or IV contrast unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis and head. In patients for whom CT scans with contrast are contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRIs of the chest, abdomen, and pelvis with a non-contrast spiral CT scan of the chest may be used. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. For further information see section 4.5.5.

[j] Tumor assessments performed as standard-of-care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. The same radiographic procedure must be used throughout the study for each patient. Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will be performed at baseline, every 9 weeks (approximately every three cycles) following randomization for 54 weeks, and every 12 weeks thereafter, with additional scans as clinically indicated. Assessments will continue until disease progression or loss of clinical benefit (whichever comes later). Tumor assessments should continue regardless of whether patients start new anti-cancer therapy in the absence of disease progression unless they withdraw consent. Patients who discontinue study treatment for reasons other than disease progression (e.g., toxicity), should continue to undergo scheduled tumor assessments as if they were on the protocol schedule until the patient dies, experiences disease progression per RECIST v1.1, withdraws consent, or until the study closes, whichever occurs first. If an optional biopsy is to be performed at approximately the same timepoint of a tumor assessment or as a result of the radiographic determination (e.g., response or progression), samples should be acquired after all imaging scans have been performed, if at all possible. Investigators may perform additional scans or more-frequent assessments if clinically indicated. After the first five cycles, one of three cycles may be delayed by 1 week (28 days instead of 21 days for one cycle) to allow for vacations.

[k] Complete physical exam includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[m] ECOG performance status, limited physical examination, local laboratory assessments, and CRP assessment may be obtained ≤ 96 hours before Day 1 of each cycle (note: CRP at Cycle 3 and every other cycle thereafter; see footnote x).

[n] Vital signs include heart rate, respiratory rate, blood pressures, and temperature. For the first atezolizumab infusion, the patient's vital signs should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes and 2 hours (± 15 minutes) after the infusion. For subsequent atezolizumab infusions, vital signs will be collected within 60 minutes before the infusion. Vital signs need to be collected during the infusion and 30 (± 10) minutes after the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Appendix 2 Schedule of Assessments (cont.)

[o] Twelve-lead ECGs are required as part of the screening assessment, at the end of treatment visit, and when clinically indicated. ECGs will be reviewed by the investigator to determine patient eligibility at screening. Patients with a history of clinically significant cardiac disease (including anatomic abnormality, coronary disease, congestive heart failure, abnormal LVEF, arrhythmia, or abnormal ECG) will be required to undergo a screening echocardiogram. However a baseline evaluation of LVEF should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease.

[p] Gemcitabine will be administered at a dose of 1000 mg/m2 by IV infusion on Day 1 and Day 8 of each 21-day cycle, until PD or unacceptable toxicity. Weight will be measured for dose calculations (baseline weight should be used to calculate dose unless there is a greater than 5% weight change). Day 8 gemcitabine should not be administered any earlier than Day 7, but can be administered up to Day 11. Dose modifications of gemcitabine for hematologic toxicity are allowed and will be based on blood counts obtained within 1 day prior to Day 1 and Day 8 of each cycle of therapy.

[q] For patients receiving carboplatin-based chemotherapy: carboplatin will be administered at AUC 4.5 by IV infusion on Day 1 of each 21-day cycle, until PD or unacceptable toxicity. If institutional guidelines conflict with protocol carboplatin dosing, carboplatin may be administered at a maximum starting dose of AUC of 5.

Weight will be measured for dose calculations (baseline weight should be used to calculate dose unless there is a greater than 5% weight change). For patients receiving cisplatin-based chemotherapy: Cisplatin will be administered at a dose of 70 mg/m2 by IV infusion on Day 1 of each 21-day cycle, until PD or unacceptable toxicity. Weight will be measured for dose calculations (baseline weight should be used to calculate dose unless there is a greater than 5% weight change).

[r] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. During chemotherapy plus atezolizumab/placebo the assessment at Day 15 is required at C1 and C2, thereafter at investigator discretion.

[s] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin. In countries where serum bicarbonate is not considered a standard chemistry measurement (e.g., Japan), serum bicarbonate is not required as a laboratory study in the screening or on-study serum measurements.

[t] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Cycle 1, Day 1, every two cycles during the study treatment, and as clinically indicated thereafter. In countries where urine pregnancy testing is considered a standard, urine pregnancy testing may substitute for serum pregnancy testing.

[u] Urine dipstick includes specific gravity, pH, glucose, protein, ketones, and blood. Urine dipstick and 24-hr urine collection may be performed up to 7 days before Cycle 1, Day 1. Screening urine tests performed up to 7 days before Cycle 1, Day 1 do not need to be repeated for Cycle 1.

[v] TSH, free T3, free T4, and serum ferritin should be evaluated every two cycles (starting at Cycle 2).

[w] Blood for DNA isolation will be collected from patients who have consented to optional RBR sampling at baseline, after the patient is

randomized to the study but before study treatment. If, however, the RBR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study.

[x] See Appendix 2 for details of the pharmacodynamic sampling schedule.

[y] Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti–neutrophil cytoplasmic antibody. Baseline auto-antibody testing to be collected at screening or on Cycle 1, Day 1 prior to the first dose of study drug. If re-screening is required, auto-antibody testing may be performed within 60 days prior to Cycle 1, Day 1. Baseline CRP testing can be collected up to 7 days prior to Cycle 1, Day 1. CRP and autoantibody testing to be performed on Day 1 of Cycle 3 and every other cycle thereafter.

[z] See Appendix 2 for details of the PK sampling schedule.

[aa] Additional ATA samples may be collected in patients with signs and symptoms of infusion-related reactions if clinically indicated. See Appendix 2 for details of the ATA sampling schedule.

[bb] Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). Fine-needle aspiration, brushing, cell pellets from pleural effusion, bone metastases, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation. After signing the Informed Consent Form, retrieval and submission of archival tumor sample can occur outside the 28-day screening period.

[cc] The PRO questionnaires (EORTC QLQ-C30 and EQ-5D-5L) will be completed by patients on Day 1 of each cycle and at the end-of-treatment visit and will also be completed by patients at any visits after disease progression and/or when OS is evaluated. All PRO questionnaires are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) to ensure that the validity of the instruments is not compromised and to ensure that data quality meets regulatory requirements.

[dd] Tumor specimens are required at the time of disease progression per RECIST v1.1, unless the location of the tumor renders the biopsy medically unsafe or infeasible per investigator decision. Tumor biopsy samples will be collected by core needle or excisional/punch biopsy if deemed feasible per investigator discretion. Preferably, growing lesions should be selected.

[ee] Optional tumor biopsies may be obtained at other timepoints at the investigator's discretion if patient has provided RBR consent. Tumor biopsy samples will be collected by core needle or excisional/punch biopsy if deemed feasible per investigator discretion. Preferably, growing lesions should be selected.

[ff] The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes.

[gg] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug or initiation of another anti-cancer therapy, whichever occurs first. All other adverse events will be reported until 30 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first. After this

period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported. During the chemotherapy plus atezolizumab/placebo period, adverse events are to be collected at Day 15 if a clinic visit is made.

[hh] Day 8 visit not required once gemcitabine dosing has been discontinued or if gemcitabine is not being administered for that particular cycle.

Appendix 3 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Predose	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics Plasma PD biomarker Serum PD biomarker Blood PBMC
	30 (±10) minutes after end of atezolizumab infusion	Serum atezolizumab pharmacokinetics
Cycle 3, Day 1	Predose	Plasma PD biomarker Serum PD biomarker Blood PBMC
Cycles 2, 3, and 4, Day 1	Predose	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics
Cycle 8, and every eighth cycle thereafter, Day 1	Predose	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics
Radiographic Progression	At Visit	Plasma PD biomarker Serum PD biomarker
Treatment discontinuation visit [a]	At visit	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics
120 (±30) days after last dose of atezolizumab/placebo	At visit	Serum atezolizumab ATA Serum atezolizumab pharmacokinetics

ATA = anti-therapeutic antibody; NA = not applicable; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic.

Notes: Except for Day 1 of Cycle 1, all other predose visits and assessments during the treatment period should be performed within −3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. Additional ATA samples may be collected in patients with signs and symptoms of infusion-related reactions if clinically indicated.

[a] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit 30 days after the last dose of study drug.